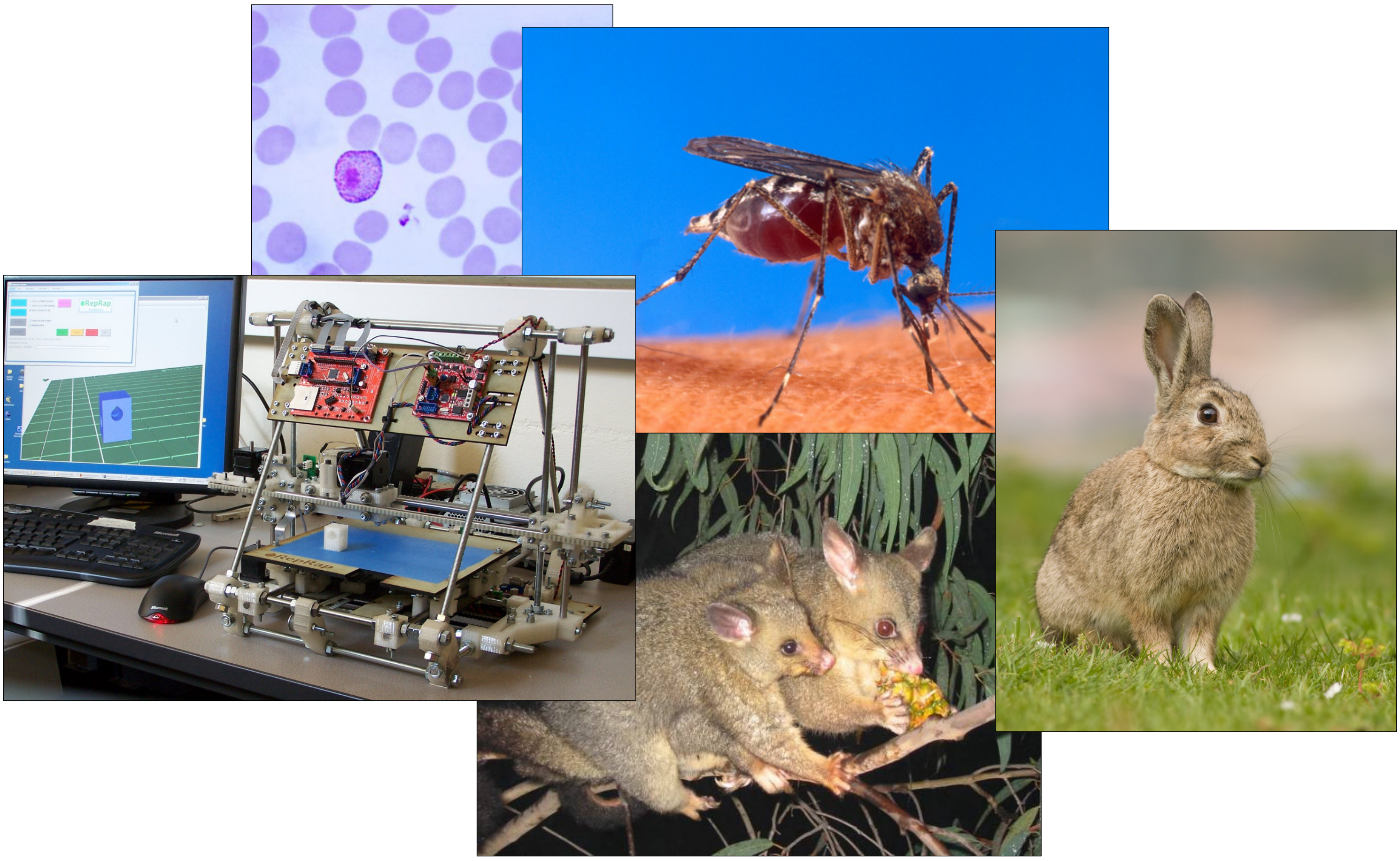
Designed to get away

Issues and implications arising from disseminating, autonomous, reproducing technologies



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Executive Summary

A new class of technological object has emerged. We can now document several artefacts that are designed to exceed the passivity our technologies have been possessed of and their governance based upon. So far, they are overwhelmingly located within biotechnology (although effort continues in other fields). These can be grouped under the broad heading of DARTs: disseminating, autonomous and reproducing technologies. This phenomenon deserves investigation and analysis. Arguably, the policy and scientific communities involved deserve the support and involvement of the ELSA community, too.

DARTs are most commonly produced in new forms of biological control. Many of these involve the genetic modification (GM) of pathogens or invasive species (pests) to achieve their control. Two illustrative cases are presented in this report. The first example describes how New Zealand researchers pursued national interest by attempting to construct a GM parasite to control feral possums by infertility. The second is a striking contrast, describing several very different research programs around the world well underway to producing mosquitoes that will either a) work to reduce wild populations that bear serious disease (e.g. malaria, dengue), or b) completely replace wild populations with a strain that cannot transmit disease.

An analysis of these two examples reveals a suite of issues that require dedicated research and, indeed, policy response. Artefacts with unprecedented powers of autonomy, movement and replication will not sit comfortably within existing frameworks of social governance.

Theoretically, DARTs will have to be accommodated into scholarly understandings of the ordering of society, and particularly the manner in which it attempts to exercise power and discipline over non-human elements like technology and wild or ecological nature(s). How contemporary theories of governance can accommodate devices with such a degree of agency, particularly in their use in managing elements of nature and society that themselves are difficult to govern (pests, disease), emerges as a research priority.

DARTs are particularly prone to causing international disputes. Designed to multiply and spread throughout the environment, DARTs will not respect national borders. Conflict may arise because different nations will often have very different valuations of and objectives for the organisms at which DARTs are targeted. Possums are pests in New Zealand, for example, but valued biodiversity in nearby Australia. Similarly, even when the objective for a DART may be shared across national borders (e.g. disease control), the nature of the DART (e.g. a GM insect), may be accepted in one nation but not in its neighbour.

Many DARTs are products of genetic modification, and hence will fall under relevant biosafety legislation, including the Cartagena Protocol at the international level. However, the Protocol has serious shortcomings in its ability to handle the unauthorised spread of GMOs that many nations may feel obliged to deploy against serious, urgent threats to human welfare (and perhaps biodiversity), such as malaria and dengue. Several important nations remain unbound by the Protocol, in any case. Furthermore, not all DARTs are produced with *in vitro* manipulation of genetic material, and may therefore escape the coverage of the Protocol and national legislation. Finally, DARTs may be recognised variously as diseases, pests or endangered species in their own right, and thus triggering a variety of legal instruments in which the priority of application is not clear. Many of these domains are currently undergoing reconfiguration as well, as current arrangements being shown to be insufficient. This legal entanglement, and the regulatory gaps that result, demands scholarly and policy action.

Many DARTs are designed squarely with public good goals in mind: the effective and environmentally-friendly suppression of disease and conservation of threatened species being the main targets so far. Nevertheless, they are radical technological interventions that have large uncertainties about them; they may pose risks to health and environment in themselves. Moreover, given their unique combination of properties, their first release (including experimentation to reduce uncertainties) may very well be an irreversible introduction to the world. Given their reproductive potential, safety measures and known properties may be made redundant or inoperative thanks to evolution.

Ethical, risk and decision-making frameworks may very likely have to be adjusted in response to DARTs. GM mosquitoes for disease control mark a particularly acute rendering of the problem. Here, DARTs uniquely offer plausible benefit to some of the world's most underprivileged humans (by the alleviation of serious infectious disease) – whose continued suffering is highly certain otherwise – but also pose, at the very least, considerable uncertainty over safety to the environment, or at very worst, absolute certainty of the destruction of a limited portion of biodiversity. Frameworks like the Precautionary Principle work to maximise the protection of both environment and humanity, and depending on formulation, may be ill-suited to the difficult tradeoffs the use of DARTs may demand. This requires urgent attention.

Culturally, politically and institutionally, the creation and use of DARTs around the world is a fascinating and under-explored topic. DARTs are exemplifications of local and global attitudes to wild biodiversity and nature as a whole. These attitudes often differ across geopolitical or cross-cultural boundaries. The mechanisms by which these audacious research programs create legitimacy, for their own imagination as well as for the political arrangements that host them, are rich topics for critical sociological investigation. Language employed to describe target 'problems', and indeed editorial and epistemic norms applied to their discussion create regimes of credibility and taboo that need to be opened up and discussed. Importantly, the institutional and political setting in which DARTs are being created, e.g. techno-friendly philanthrocapitalism, policies of neoliberalism and global development, has led to intriguing and sometimes questionable practise that demands inspection.

Finally, and fascinatingly, there are hints that concerns about safety and responsibility may have penetrated deeply, although heterogeneously, into the scientific and technological community. What may be emerging is an epistemic culture that is attempting to reconcile the uncertainties and contingencies of necessary intervention (technological or otherwise) against urgent, certain but stochastic threats to humans and biodiversity.

1 Introduction

One of the most important legitimating tenets of biotechnology is that its products, particularly genetically modified organisms (GMOs), will not spread out of control. Certainly, this is a contested claim, but it is nevertheless at the heart of the moral and legal infrastructure that today allows GMOs to be brought into existence and used in society. In fact this principle is common to many new technologies, rhetorically and constructively. The 'grey goo' of nanotechnology, for example, is now commonly declared as impossible, but it has also become a forbidden goal within the research community itself. Nevertheless, there are now several instances of research in biotechnology where the end goal is, explicitly, a GMO intended to be released into the world, to persist, disseminate and replicate. These GMOs are designed to get away. Many are directed at invasive species (e.g. exotic pests), but others at vectors of human disease, or indeed wildlife diseases. These biotechnologies are examples of a broader class of technology that are designed to spread into the world by autonomous movement and reproduction, and perform specific tasks while they are out there. I broadly consider these under the heading disseminating, autonomous, reproducing technologies (DARTs). Biotechnology is currently the only technological platform from which DARTs may be launched in the near or immediate future – hence this report is primarily focused on GM biocontrol – but it is expected that many of the fundamental issues encountered here will be common to all future forms of DARTs.

Constructing and releasing DARTs is an action rather different, morally, legally and politically, than most other technological actions in our history. For instance, while one may be considered responsible for the consequences of operating a piece of machinery, in general once the machine is switched off the processes of consequence stop, at least in its direct and immediate effects. Although secondary, contingent effects may still be ongoing, liability can thus be simply and practically limited, a moral architecture is built fundamentally around the “off” switch, or more fundamentally around the machine’s inherent tendency toward inanimation. The direct and immediate consequences of DARTs, however, will be ongoing. Furthermore, because these devices are living and replicating, they may evolve. Since design features are fundamental to the architecture of control (and the corresponding "shadow architecture" of the technology's moral legitimacy to exist within society), DARTs represent not only a loss of control over action and location, but also over their very nature. And although we often forget – because we so rarely must consider it – control over the numbers of devices we produce is usually helpfully limited by the dynamics of decline. With devices capable of replication, we may face the somewhat novel challenge of having more items than we started with. Although we can consider a number of technologies that do not conform well to this ideal of a device that is fixed in time, place and activity (e.g. PCBs, nuclear power, etc), in each case there is a moral (and thus legal and political) distinction at the heart of the way we govern their use - accidental escape, although problematic, is not the same as intentional release.

Control and governance is at the heart of the challenge presented by the dawn of DARTs. Exactly what revisions to our forms of governance will be required? We are not particularly well equipped to manage technologies that are, in fact, agents. How do we cope with agents designed to have so much agency in the real world, especially given that so much of the mechanisms of governing agents-in-society requires them to be human subjects that we can shame, educate, indoctrinate or acculturate, or imprison, exclude, extract from or indeed, finally, kill? And how do we deal with rule-making for agents that may freely cross cultural and jurisdictional borders?

This evaluative synthesis looks at some of the challenges in governing DARTs we may soon have to grapple with. It considers DARTs broadly under the current turn to 'governance', then explores GM biocontrol, using two very different examples as case studies. My intention is to draw what lessons as can be extracted from this short appraisal, but moreover, articulate particular issues that will need dedicated work, and may form the basis of a rich and important agenda in research and policy-making for many minds in the years ahead.

2 Governance

The idea of "governance" is now a prominent conceptual framework in which to tackle the project of governing society, invoked at local, national and regional scales (Lyall and Tait 2005), at least in the democratic West. Multiple as the meanings of "governance" may be (Newman 2001), all mark a shift in the social contract society establishes with its government, in which centralised "command and control" has given way in the face of disenchantment and disenfranchisement with established modes of democratic rule, undermined by the rise of pervasive and endogenous risk as an ordinating theme (Beck 1992), and a general recognition of complexity, contingency and interconnectedness in the real world that overwhelms the capacity of reductionist, silo'd epistemological and policy models. No one governing body can tackle 'real world' problems without the recruiting the knowledge and resources of others (Kooiman 1993). Governance is therefore conceived – and advocated – as a network of regulation, institutions and practises of authority and power (Lyall and Tait 2005). Concomitantly, non-state actors are welcomed as partners into the work of ruling society, or at least recognised in the project, and participatory and deliberative forms of decision-making (contested though they may be) become increasingly legitimate ways of making policy (Pellizzoni 2003; Smith et al. 2005; Finke 2007).

Neatly phrased, governance reflects a shift from "power over" to "power to" (Pierre and Peters 2000) – the centralised power-claims of a state government are diluted, and power is actively pushed out to NGOs, public-private partnerships, businesses and citizens. However, this pithily-phrased observation, popular among politically-engaged disciplines like political science, critical geography and the like, reflects an oversight that social sciences often fall victim to, namely, the agency of non-human things. In fact, society is constituted of both human and non-human, made and natural, tangible and intangible components, including those artefacts that we call technological (see Box 2.1). If the common project is now to push the power to govern out to the constituents of society, do we really mean to push the power out only to people? What of the non-human? What of the technological? Do we not, in many ways, do this already? Are there limits to how much we can do so, and are they changing? Untangling these issues with philosophical rigour is beyond the scope of the report, although the importance of doing so is one of its conclusions (section 5), and the answer to the last question is an emphatic, "yes". However, used as a heuristic device, the thorny question of "how do we handle technologies with power?" – or perhaps, "how much power do we wish to give technologies?" – opens up the unique nature of DARTs, and the particular challenges they bring for their governance.

Box 2.1 – The more-than-human composition of society

The more-than-human composition of society is well recognised in many scholarly perspectives, ranging from sociological and political enquiry such as Actor Network Theory (Callon 1986; Law and Hassard 1999) and calls to consider 'a parliament of things' (Latour 1993; Bennett 2005), to ecological sciences like human ecology and conservation biology and even recent economic turns to ecological dependence like ecosystem services and the discipline of ecological economics. More particularly, insights from work in the late 1980 and early 1990s convincingly demonstrate the co-constitutive relationship between technological artefacts and technological systems and society (Bijker et al. 1989; Bijker and Law 1994). In short, although society is a) most comfortable believing that it creates technological devices in service of itself, and b) most comfortable in considering nature as something external to its ordered, regulated existence, the structure and action of technologies and ecology nevertheless create, act in and change that very same society. The fabric between the social and the material is seamless (Callon 1989). This is important, because DARTs merrily transgress these illusory divisions right from the very start. Throughout this report I intend references to 'society' and its order (the objective of governing) to include both social and material things, whether the 'material' be technological or ecological, whether the 'social' be tangible or intangible.

Technological artefacts are generally recognised having, or being ought to have, 'merely' passive structuring and facilitating roles. Technology *should* work *for* us, after all. In some ways, governance – particularly the governance of technological risk – is about ensuring that passivity. It is the drive to overcome technologies with too much agency (e.g. nuclear radiation, BSE, etc) that forms one of the motivations in the push to governance. Even amongst societies with very different political traditions, in which a turn to "governance" is neither manifest nor likely, there is an inherent demand for the passivity of made things. At all levels of society, there is a general desire for our technological artefacts to stay within the confines we have deemed acceptable. Governing technologies successfully means somehow – with control vested either in people or in the design of the object itself – artefacts must not wander out beyond the special places we have allocated them, and they should not perform actions that are not tightly specified for them within those special places. And there shouldn't be more of them than we start out with. In contrast to people, empowering devices "to" is far from unproblematic. We want to maintain "power over".

3 DARTs and other artefacts

The question of reproduction, particularly, but also autonomy and dispersal, invite a quick heuristic division of DARTs. This basic typology splits the living, *biological* DART from the mechanical, in which we can also include nano-mechanical artefacts. Each have their own history.

3.1 Mechanical DARTs

With the challenge of governing artefacts foremost in mind, it is perhaps a matter of relief that they have been conveniently passive for most of our history. Not everyone has shared that sentiment. For more than a century western civilisation has entertained the notion of sophisticated machines that will not only perform complex tasks independently, navigating the world on their own, but that might also take on one of the most distinctive characteristics of living things, the ability to reproduce (Freitas and Merkle 2004). It has done this both imaginatively and practically. The imaginations have often been dystopic.

Nevertheless, devolving action, authority and production – strictly bounded – to our devices has recurred in our society as a promissory theme. Effort has often been intense, but progress has been uneven. Mechanisation, generally, has proceeded at a voracious pace since the Industrial Revolution of 1800s. While the challenges in designing artefacts that are 'intelligent' enough to independently cope with the complexity of the real world are still large, recent advances in robotic technology that suggest a certain threshold has been crossed (Gates 2007; Lavine et al. 2007; Bar-Cohen 2009; Singer 2009; Barlow et al. 2010; Cho et al. 2010). Highly independent machines, intelligent, capable of making decisions for themselves, and engaging in a wider range of behaviours are now becoming serious prospects that demand our attention.

However, daunting challenges remain in building self-replicative devices at any scale, macro (Yim et al. 2007; Lee et al. 2008) to nano (Sipper 1998; Smalley 2001). Some of the principles have been well developed though. Hungarian-American John von Neumann is famously associated with replicating machines, having pioneered a theoretical (mathematical) basis for self reproducing automata in the mid 20th century (Von Neumann 1966), ideas that have been extensively elaborated upon since (see Freitas and Merkle 2004). Building something in the real world (as opposed to digital worlds) has been much more challenging. This is not to declare reproducing machines an impossibility. Impassioned enthusiasts Robert Freitas and Ralph Merkle, for example, mount a spirited, well-substantiated defence in their widely-cited treatise on 'kinematic[1] self-replicating machines' (Freitas and Merkle 2004, especially chapter 6). There is substantial effort underway on a variety of scales, and some early prototype systems have been developed (see numerous examples detailed in Freitas and Merkle 2004).

For many, especially in the face of nightmare scenarios like Drexler's 'gray goo' (Drexler 1986), the lack of progress on replication is something of a relief. In fact, so charged a concept is replication that a significant amount of (political) work has been done to remove the imminent prospects of nanotechnology from ideas of replication from nanotechnology proponents themselves (see, for example, the statement in Annex D of the UK's Royal Society and Royal Academy of Engineering report on nanotechnology prospects (2004), page109). Expectations of success amongst replicator developers are so high – and/or the recognition of wisdom of a precautionary posture is so well established – that the research community has even developed a set of guidelines for the development of replicating devices that explicitly work to shut down the possibility of a runaway scenario (Jacobstein 2006); not coincidently, they follow similar lines to the US's National Institute of Health's guidelines for recombinant DNA technologies (Freitas and Merkle 2004; National Institutes of Health 2009). Crucial to our concern with governance, these and other normative visions are emerging strategies of control that distribute right across the seamless fabric between the material and the social. They involve both disciplining

[1] i.e. working in the real world, as contrasted with digital environments.

and self-disciplining of human inventors, through recommendations for commercial and intellectual exchanges, ethical oversight and communication, and sometimes calls for the outright abandonment of certain development programs (e.g. Joy 2007), and also the construction of governing features into the machines themselves (e.g. centralised control, engineered under-competence in reproduction, etc).

But for now, replicating machines remain an interesting, developing idea, one for which we have not yet been forced (by imminence) to regulate, but merely discuss. In fact, in the face of the 'industry' of technological critique that has amassed in recent years, areas like nanotechnology are perhaps receiving too much attention to particular speculations about their future manifestations and governance (Nordmann 2007; Nordmann and Rip 2009). Overdeveloped too may be the years of science fiction that have entertained us with frights and horrors of replicative machines taking over us.

Taking the view from a point immersed in the mechanical arts, then, one might conclude that disseminating, autonomous and reproducing technological devices (DARTs) – intentionally made artefacts that disperse, reproduce and work, by themselves, for us – might seem to remain an imaginary figure rather than material reality. Perhaps then, we should lay aside questions about governance arrangements for these not-yet-here upstart objects, these artefacts with too much agency.

Two domains of technological achievement stand against this move, however. Firstly, in computing and information technology, software 'devices' can now be routinely constructed that perform useful work for their human clients and self-replicate in a wholly human-made 'world' of electronic information space. The historical development of computing is in fact deeply intertwined with reproducing software, (a class of replicating 'agents' known as cellular automata), through the foundational work of von Neumann (Aspray 1990). Self-replicative software can now perform work for both sanctioned and criminal ends (Guessoum et al. 2006; Grizzard et al. 2007; Grottke and Trivedi 2007; Dressler and Akan 2010; Huhns 2010). As society becomes more entangled with digital works, these autonomous artefacts are indeed socially significant. The ability of these agents to exceed the boundaries (of geography, of borders) to which we are accustomed in the physical world is already a challenge for governance the world over. But as they are still contained within a particular, artificially sustained environment[2], they are something of a special case.

3.2 Biological DARTs

More interesting to the topic of this report are developments in biotechnology that push quite beyond the 'headline grabbers' of GM crops. These biotechnological DARTs involve a surprising range of organisms, modified to effect some change in the population of free-living organisms (usually, but not always, a reduction). As technological solutions, they are heavily dependent on the ability of living things to disperse themselves and reproduce. First, however, it is necessary to examine how they differ from existing forms of biological artefacts.

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[2] Even though some of their effect may plausibly transformed into the 'real' world by linkages with physical entities. In yet another example of convergence, as machines become more 'intelligent', independent from human operators, and increasingly Internet-enabled, the real-world impact of worms and other autonomous, replicating software may become intensified.

3.2.1 Biological artefacts

Biology, obviously, offers the most exquisite and truly stunning variety of entities capable of performing complex tasks in a complex world, without external central control, and possessing the capability to reproduce. Humans have requisitioned this ability in a relatively modest list of examples – domesticated animals, plants and microbes, traditionally. As this report explores, we are extending that list in new directions and for new purposes. Are these organisms artefacts? They are, after all, modifications on an essentially natural originating stock, a use (with elaboration) of 'found biology'. Eric Katz, although addressing more questions about ecosystems and environments than individual organisms, argues strongly that biological systems altered and arranged for human utility are indeed artefacts (Katz 1993). Helena Siipi (2003), points to Callicot's (1980) categorical declaration that domesticated animals, at least, are indeed artefacts. Domestication, then, seems a useful point to look at ways in which we have historically established modes of governing over artefacts capable of, at least originally, a great degree of autonomy, dispersal and reproduction.[3]

As might be expected, a definition of domestication is a site of contest among scholars (Cassidy 2007), with emphasis placed by some upon the mastery of humans over wild biology (Bökönyi 1989; Clutton-Brock 1994; Russell 2002), and others the co-evolution and co-production of non-humans, humans and thus society (Leach 2003; Clark 2007; Haraway 2008). Similarly, the process of domestication, of various species, as an antecedent, consequence, or contemporary and co-productive shift to settle patterns of human life are unclear and details subject to scholarly debate. It is enough for this report to note that the relationship between domesticated biology and human society is at least to some extent recursive, both in the notion of who domesticated who, but also in the ongoing performance of the socio-natural order of modern society.

Domestication is generally thought to be facilitated by close association and possession, and control of breeding for the benefit of humans (Clutton-Brock 1999). The creation of order around domesticated biology, then, can be understood to turn upon two inter-operating factors, namely control over the nature of the organism by virtue of extending influence over composition, and containment of the organism. Their compositions, and hence natures, have been manipulated via artificial selection, first by traits understood at the phenotypic level (Leach 2003), and now increasingly by accessing molecular genetic information for marker-assisted breeding (Collard and Mackill 2008; Thomson et al. 2010) or rational alteration of genetic composition itself by genetic modification. On the other hand, clipped wings, fences, and buffer zones are all techniques that have been deployed to ensure containment

[3] There are of course other uses of biology. We have wildlife tourism, religious significance, recreational hunting and pragmatic exploitation as resource. As the recognition of the need to manage these resources has grown, society has moved to govern this form of life (in many different times and places, not just recent western history). Indeed, natural resource management is one of the 'front lines' in the turn towards governance. But while these uses of biology may indeed entangle these biological agents in heterogeneous webs (e.g. cyborg fish; Holm 2007), they remain essentially wild. They are not artefacts (although the ecosystems in which they live may be). The distribution of governance centres mostly on humans and institutions, although notable exceptions to this might be efforts at exclusion (e.g. fencing, quarantine), extermination, and in some cases where the organism is intelligent enough, learned aversion techniques.

of these almost-machines. Breeding-in passivity has also been useful for containment; for example, docile temperament is a desired trait among cattle for ease of management, productivity and safety. Conversely, containment has been essential in allowing us to shape natures. Neutering, separation of sexes, races and bloodlines and structured breeding programs are restrictions of not only the living subject (i.e., the plant, the animal, the microbe), but of genes and thereby natures. Regulating genetic flow by contained, controlled reproduction permits us to influence natures. Containing reproduction also, importantly, allows us to maintain an order of numbers. We may rarely hear of an invasive horde of someone's sheep devouring all in its path, for example, but history has certainly provided us with a horde of rabbits devouring a continent (Australia; Rolls 1969): one species is well governed, the other is not. Reproductive containment is also a source of wealth. The economic value in a prize bull lies not so much in its carcass as in the ability to profit from its genetic potential, via the careful regulation of its reproduction. So, not only are we adverse to our living artefacts escaping, we take care to guard against their unauthorised reproduction and spread.

While the composition of nature and containment are used to facilitate the other, they are also used to compensate for a lack of the other. A well-trained animal may not require restraint by leash or fence, for example, requiring a certain nature that has been instilled by breeding (genetic composition) and learning (neural composition). We have not taught plants to be so well behaved, and resort to buffer zones and so-called terminator technologies to guarantee constraint. Nigel Clark (2007) links domestication with Foucault's idea of modernity's imposition of a "grid of intelligibility" on the world, where the "grid" imposed by domestication pulls non-human life into the ordinating rationale of our modern society[4]. Citing diseases and invasive (pest) species, he argues that the ability of living things to move around with a will of their own and to reproduce – that is, whose compositions are not controlled and whose actions 'exceed' our containment, and are thus *not* domesticated – has long been a problem for governing. To maintain the order of society, if our living artefacts retain too much agency, we stake steps to increase our power over them by containment until such time (if ever) as they may be disciplined. In contrast to our made and inanimate machines, that in late modernity troubled us by revealing just how animate they can in fact be, we have always known of the threat posed by living artefacts whose natures we have 'steered' rather than composed.

But the play between constructing a known, customised nature and containing something whose nature remains (to some extent) wild is also the distribution of governance of technologies between artefact and human. It is the human subject that disciplines themselves to fence in their valuable livestock, that seeks to hold onto their valuable seed stock, that holds their experiments within special, filtered, restricted buildings. It is society that imposes restrictions on where the non-human organism can be used, can be experimented and played with, can be created. The risks of unknown natures was explicitly recognised in the Asilomar conference in 1975, where careful containment was recommended as a means to combat the uncertainties inherent in the very new prospect of genetic modification (Berg et al.

[4] A grid of intelligibility refers to the deep, culturally-derived frameworks within which we construct and evaluate theories about the world, and hence structures the programs of action we (or any actor in society) undertakes. Clark is particularly interested here in noting the economic utility that pervades modern thinking, and the modern grid involves "a calculus to life and labour such that the value of all things can be known and the costs or benefits of any action discerned— preferably in advance" (Clark 1990:50).

1975), and continues as a central theme to this day (National Institutes of Health 2009). A vital term of the social contract that has allowed the commercial release of GM crops, for example, has been the use of buffer zones[5] and segregation, and special provisions for traceability and detection to ensure these techniques work. One of the earliest and widely advertised hopes of biotechnology, seeding the world with microbes engineered to eat oil spills and other pollutants, wrestled painfully with public concerns over open release, and although technical failure largely allowed the issue to be forgotten, an anticipation of poor public and regulatory reception certainly did not work to boost investment in the field (de Lorenzo 2001; Watanabe 2001; de Lorenzo 2010). Even in the radical project of synthetic biology[6], in which by some definitions the nature of living things is to be constituted completely artificially, strict containment is demanded and promised in the name of governance and learning from past technological mistakes (Tucker and Zilinskas 2006; Yearley 2009).

4 GM biocontrol

Against this backdrop, then, we might consider it unusual – even surprising – that there are now serious moves afoot to construct and release genetically modified organisms (GMOs) whose very utility lies in their ability to disperse themselves in the world, perform specific and often complicated tasks, and to replenish their numbers by reproduction without our involvement. In fact, not only are moves afoot, but in at least one case the technology has already been field tested (Torres et al. 2001; Angulo and Barcena 2007). The living agents being recruited to this task range from viruses (sitting at the edge of 'life'[7]) and parasitic nematodes to vertebrates like fish. Like domesticated species, they are both in part *made* artefacts, but at the same time still 'found' biology, first brought into being and constituted by forces devoid of human intention, and much more so than domesticated species. They remain usefully wild, but at the same time, because they would not exist without our construction, they are our machines. The problems at which they are targeted are exactly those parts of biology that refuse to come under containment and are beyond our ability to control composition: diseases, pests, and wild creatures. These problematic forms of life, at first glance, sit outside of our society's "grid of intelligibility" (Clark 2007), dwelling outside the civilised structures of (Western, at least) social orders, escaping being disciplined into particular spaces and practices. It is, perhaps, ironic that these problems of governability are being tackled with technologies that may themselves be so hard to govern.

An incomplete survey of DARTs created for biocontrol is listed on the next page (Box 4.1.1). The following sections take a closer look at two applications of biological DARTs. In the first, we examine recently discontinued work in New Zealand that tried to create a biological 'magic bullet', immunocontraception, for an invasive species, the Australian brushtail possum. In the second, we survey the very global concerns about infectious mosquito borne diseases, and the range of DART applications based on genetically modified mosquitoes that are being rapidly developed to tackle them.

[5] This social contract is of course contested, not universal, and may indeed been seen as a historical hiatus in a greater battle over governing technology. The utility of buffer zones is understood as being ecological and (commercially) proprietary. The effectiveness of buffer zones and other practises of cultivation in containing GM crops is, of course, subject to debate.
[6] This report views synthetic biology as contiguous with or part of the existing category of biotechnology.
[7] Viruses may be otherwise excluded from the notion of 'living things' – they do not respire, and they require the machinery of living cells to reproduce. For simplicity, I beg the reader's indulgence here.

Box 4.1 – An indicative list of biological DARTs around the world.

Developed from (Angulo and Gilna 2008b). Note this list is necessarily incomplete (see section 5.2)

DART	Target	Objective	Refs.
Myxoma virus	European rabbit (*Oryctolagus cuniculus*)	Transmissible vaccine for European rabbits against myxomatosis and rabbit hemorrhagic disease	(Bárcena et al. 2000)
Myxoma virus	European rabbit (*O. cuniculus*)	Reduction of invasive rabbits by immunocontraception	(Van Leeuwen and Kerr 2007)
Murine cytomegalovirus	mice (*Mus musculus*)	Reduction of mice in agricultural landscapes to suppress episodic population explosions by immunocontraception	(Hardy 2007)
Nematode (*Parastrongyloides trichosuri*)	brushtail possum (*Trichosurus vulpecula*)	Reduction of invasive brushtail possums by immunocontraception	(Bárcena et al. 2000)
Insect commensal bacteria	insect borne disease (malaria, sleeping sickness, etc) and their vectors	Prevention of infection by rendering insect vector resistant to pathogen	(Coutinho-Abreu et al. 2010)
Microbes (fungi, bacteria)	weeds (various)	Improved lethality, host preference, etc of biological control agents	(Federici 2007)
Selfish genetic elements	weeds (various)	Reduction of populations by inducing sterility in male parts.	(Hodgins et al. 2009; Rector 2009)
	insects (various)	Reduction of populations by causing sterility, altering sex-ratio, etc.	(Gould et al. 2006; Gould and Meagher 2008)
Daughterless carp (*Cyprinus carpio*)	self; invasive fish, particularly European carp (*Cyprinus carpio*); also considered for other species	Reduction of populations by altering sex-ratio	(Thresher and Bax 2003)

Anopheles, *Culex* and *Aegypti* mosquitoes	malaria *(Plasmodium* spp.), dengue, yellow fever, Chikungunya viruses	Mosquitoes rendered incapable of carrying and/or transmitting specific diseases	(Gould and Schliekelman 2004; Coutinho-Abreu et al. 2010)
	self	Reduction of mosquito populations by interference with reproduction	(Thomas et al. 2000; Fu et al. 2007; Fu et al. 2010)
Wolbachia mutant	insect hosts, notably the dengue vector, *Aedes aegypti*	Insects rendered incapable of hosting or transmitting disease agents	(McMeniman et al. 2009)
Insects (various)	self; insect pests developing resistance to insecticide	Sensitization of insect populations to insecticides	(Lapied et al. 2009)
	self; insect pests developing resistance to insecticide	Release of insects sensitive and reproductively deficient into populations developing insecticide resistance	(Alphey et al. 2007)
	weedy (plant) species	Enhancement of insect biocontrol agents to destroy weeds	(Rector 2009)
	self; Medfly (*Ceratis capitata*), Cotton pink bollworm (*Pectinophora gossypiella*) and others	Reduction of populations by interference with reproduction	(Gong et al. 2005; Simmons et al. 2007)
Plants (various)	self; various weeds (e.g. *Striga hermonthica*)	Spread of transgenically female-sterilised weed via gm pollen	(Rector 2008)
Trojan sex chromosome	self; invasive fish, (also considered for other animals)	Reduction of populations by altering sex-ratio	(Gutierrez and Teem 2006; Cotton and Wedekind 2007)

4.1 Possum control in New Zealand

Australian brushtail possums[8] (*Trichosurus vulpecula*) were introduced to New Zealand in the 1800s to establish a resource for a fur trade. Initially protected, by the 1980s possums were widely recognised as a pest (Green 1984; Wright 1992) and subject to control efforts. In 1992, as biotechnology bloomed across the world, the New Zealand government established a research program to develop a biological control for the possum, one that exploited biotechnology's promise to provide a tailored, permanent solution (see Box 4.2.1). Of all the options considered, one project soon became a prominent front runner: a disseminating form of immunocontraception vectored by a parasite, the nematode *Parastrongyloides trichosuri*. Despite several years of work, substantial investment and the persistence of possums as a threat, this DART project has recently been quietly shut down.

The clever idea behind immunocontraception is, essentially, to 'trick' the animal's immune system into recognising reproductive structures (hormones, sperm, egg, embryo) as foreign invaders – the immune response either destroys or blocks essential steps in the reproductive process, ideally with minimal suffering to the adults (Seamark 2001)[9]. For biocontrol, the immunocontraceptive approach relies on using genetic modification of an infectious agent to present a reproductive protein in a context in which the body will be mounting an immune defence. The reproductive protein would thus come to be seen immunologically as an invader, essentially vaccinating the animal against pregnancy. Choosing an infectious agent that is specific for the target pest is essential for spreading the contraceptive effect (a crucial property of a DART), but also in limiting it to the target species only.

The biology of *P. trichosuri* made for a remarkable fit with the requirements for a candidate for GM biocontrol in New Zealand. First and foremost, the possum host is a marsupial, vastly distant in evolutionary terms from any native or domestic animal in New Zealand. There was no other host that could be infected within the nation's borders; no other animal was at risk of becoming infertile. A DART based on *P. trichosuri* was thus considered exclusively targeted at the pest possum. Even better for a permanent solution, *P. trichosuri* has an unusual bimodal life cycle (Stankiewicz 1996). In one mode, the nematode can reproduce indefinitely in a free-living, soil dwelling form. Upon encounter with a possum, the nematode can enter into a parasitic mode, and complete its life cycle thus. A free-living population of modified *P. trichosuri* would therefore create a sustained barrier to possums in that environment, even if unaffected possums should recolonise an area in which they had been eliminated.

The ability to propagate the nematode in a medium that did not require a living host greatly simplified laboratory handling, including the procedures for genetic modification (Grant et al. 2006b). Heritable genetic transformation of *P. trichosuri* was demonstrated (Grant et al. 2006a), something of a technical achievement in itself. Although the inheritance is thought to be extra-chromosomal, it is reliably inherited across several generations in the lab. (Transgenic material that sits outside

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[8] Possums are marsupials, evolutionarily distinct from placental mammals like humans, cattle, lions, etc., by giving birth to small, poorly developed young that must continue development in a special pouch. With only a handful of exceptions, (e.g. opossums in the Americas, tree kangaroos in Papua New Guinea), they are endemic to Australia, where they make up the vast majority of native mammals. Many of these marsupials are endangered, and many have already gone extinct.

[9] See Appendix 1 for a history of the idea and institutions involved in its development.

of the host chromosomes (i.e. extra-chromosomal) is generally unstable and lost after a few generations). Researchers discovered they could use the semi-domesticated Australian sugar glider, *Petaurus breviceps*, as an alternative (easier) laboratory host (Nolan et al. 2007).

Infection is through the skin (Stankiewicz 1996), and appears to be relatively easy to achieve: captured possums can be infected simply by squirting a watery mixture onto the animal's belly (Grant et al. 2003). The presence of the parasite in the animal stimulates an immune response, but not one that is reliably protective against re-infection (Heath et al. 1999). Not only does this feature mean that possums could receive multiple doses in the wild, but each time its immune system would be called into action – exactly the response need to make immunocontraception effective. It does not appear that immunocontraception through GM *P. trichosuri* was ever demonstrated, although several different reproductive proteins (i.e. without the worm) have been trialled in possums, with some publications reporting up to 90% reductions in possum fertility after injection (Duckworth et al. 1999, but also Duckworth et al. 2007; Holland et al. 2009).

Despite the promise, there were limitations. Results emerged that suggested individual possums can react quite differently to the immunising proteins (Holland et al. 2009), raising the possibility of resistance evolving in the pest population (Cooper and Larsen 2006). Modelling suggested that to be effective, the immunocontraceptive would have to operate at close to 100% efficacy (Tompkins 2007). Prominently, however, the risks to nearby Australia – where there are several native possums species, some of them endangered – were disturbingly high (Gilna et al. 2005).

Australia is the origin of the brushtail possum and related species – some of which are only recently described (Lindenmayer et al. 2002). *P. trichosuri* has been found in at least three other possum species (Viggers and Spratt 1995; Viggers 1997; Viggers and Lindenmayer 2000) and, in the lab, in the non-possum sugar glider (Nolan et al. 2007), which suggests that the nematode might occasionally be infectious beyond possums in the wild. The little data there is on possum parasite distribution (D. Spratt, pers. comm.), suggests that the actual dynamics of *P. trichosuri* ecology is complex. It is hard to envisage how a GM *P. trichosuri* could be detected in Australia before it had begun to do damage, and indeed, what could be done about it – from predicting its spread to cleaning-up the outbreak – is unclear.

Australia and New Zealand are separated by a three hour flight, and exchange large amounts of travellers, goods and machinery each year (Australian Bureau of Statistics 2000a; b). While possums are indeed native to Australia, they are reviled by some as a public nuisance or a pest of agriculture and forestry (Pietsch 1995; McArthur 2000; Kerle 2001). It was not hard to imagine infectious material, either in accidentally imported soil on a machine or hiking boot, or intentionally smuggled, getting into Australia.

Despite a spirited defence by the technology developers (Cowan et al. 2008), funding for the GM nematode has now ceased. Weihong (2009) suggests that anticipated controversy and resistance to disseminating forms of possum biocontrol over non-target impacts means that "a disseminating delivery system is not likely to be available for possum management in New Zealand".

Box 4.1.1 – A permanent solution

Australian brushtail possums (*Trichosurus vulpecula*) were introduced to New Zealand in the 1800s to establish a resource for a fur trade. Initially protected, by the 1980s possums were widely recognised as a pest (Green 1984; Wright 1992) and subject to control efforts. Possums are estimated to cover over 98% of New Zealand, and have had a devastating impact on the unique ecology of New Zealand (which is very different from Australia's) through habitat destruction, competition and direct predation (Cowan 1990). Possums are a host to bovine tuberculosis, and so are a major threat to the nationally important agricultural sector (dairy and beef, but also farmed deer), with a 1990 estimated risk of $NZ 2 500 million in sanitary trade barriers (Cowan 1990). Surveys now find >90% of New Zealanders recognise possums as a problem, with both environmental and economical concerns prominent in focus group responses (Wilkinson and Fitzgerald 2006).

Trapping, poison baiting etc have proven to be effective measures for population control, but are expensive, ongoing, and baiting necessarily uses toxic chemicals (Cowan 1990; Cowan and Tyndale-Biscoe 1997). The terrain in which possums need to be controlled is often rugged and remote, and baits are regularly distributed aerially, including by helicopter. Baiting, clearly, is the most tractable option for area-wide population control. The toxic agent used is sodium monofluoroacetate (or '1080'), a controversial compound that has been the focus of a campaign to be banned across the world, including New Zealand (Weaver 2003).The limits of 'orthodox' methods of control are readily apparent to wildlife managers and other 'elites', and up to 83% of public survey respondents have agreed that new forms of control are required (Wilkinson and Fitzgerald 2006).

A New Zealand National Science Strategy Committee (NSSC) was constituted in 1992, and in October of that year established "clear research priorities for biological control" of possums (Anon. year unknown). The potential for the "spectacular advances in molecular biology… to develop techniques for solving pest problems" was in the spotlight (Atkinson and Wright 1993), mindful of the directions in Australian research on the idea of immunocontraception-by-virus for solutions to Australia's invasive species woes (Tyndale-Biscoe and Jackson 1990). Biological control was nominated as the only cost effective solution (Heath et al. 1994), contrasted with traditional methods that "are expensive, and cannot eliminate the problem". The goal was nothing less than a "'permanent' solution" (quotation marks in original; Atkinson and Wright 1993).

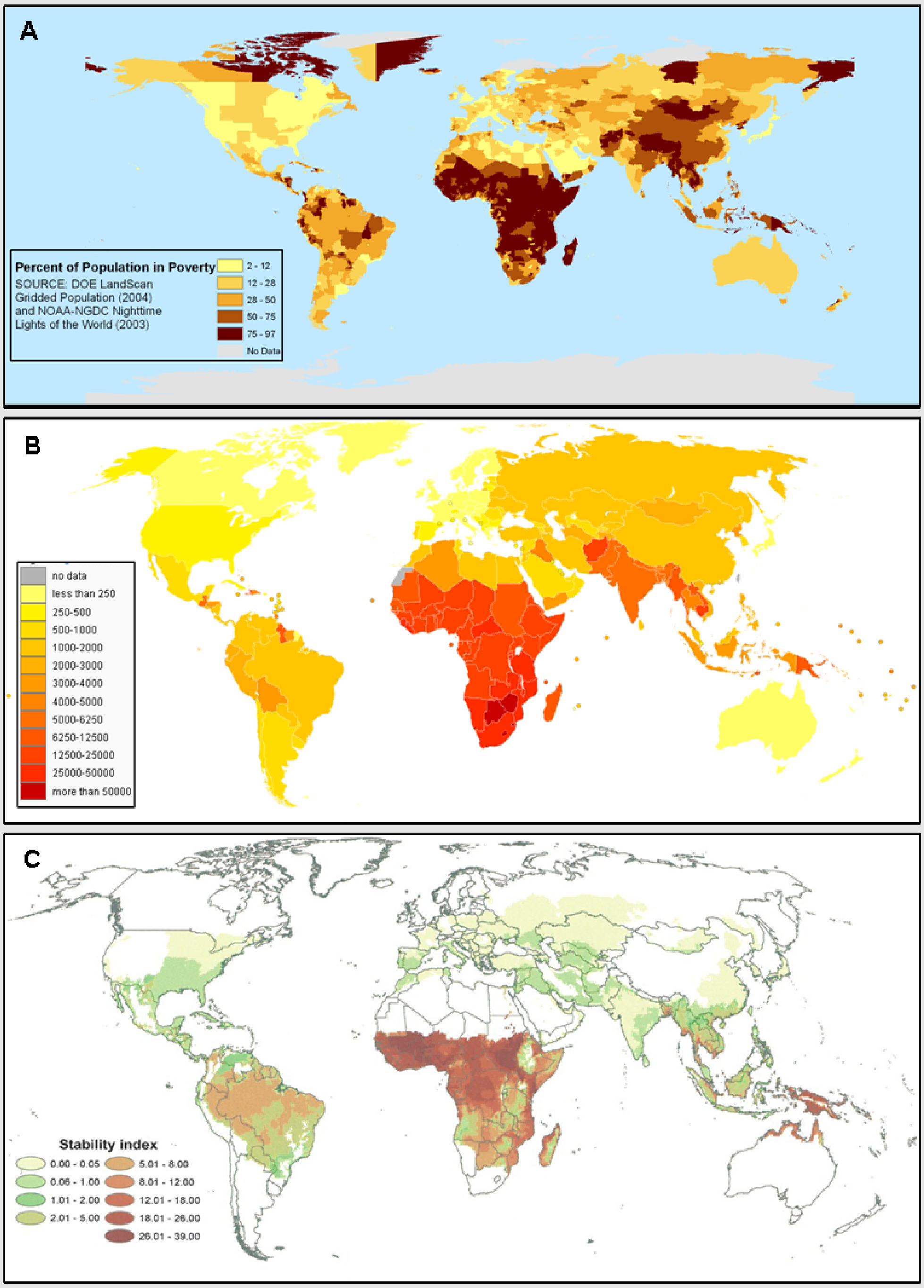
4.2 Genetically modified mosquitoes and human disease

Mosquitoes are a class of insects that are evolutionarily specialised in biting animals and feeding on their blood. Mosquitoes are widespread throughout a great many ecosystems, and feed on a wide variety of animals, and in turn are fed upon by a wide variety of organisms, including in their aqueous larval phase. They are an important feature of many ecosystems. In addition, several mosquito species have co-evolved with humans and the changes we have made to environments (e.g. agricultural irrigation) and the particular habitats we have created in our homes, villages and urban areas. Mosquitoes of various species are vectors for a variety of serious human diseases. Mosquitoes both carry infectious material between infected humans, and non-humans (so-called ‘wildlife reservoirs’). In some cases, a period inside the mosquito forms an integral part of the lifecycle of the disease-causing agent, (e.g. malaria parasite, *Plasmodium falciparum*). Malaria is perhaps the most serious of all the mosquito-borne diseases, with half of the world's population at risk of infection, and in the order of a quarter billion infections and 1 million deaths annually (the majority of them African children; World Health Organization 2008). However, viral illnesses brought by mosquitoes include yellow fever, Chikungunya and dengue and several others, and are also debilitating and often fatal. Increasingly, the endemic presence of infectious diseases like these is being linked to issues of global poverty and, thus, global injustice. More detail is provided in Appendix 2, but see Box 4.2.1 for a brief overview. While there are many points for intervention in these disease cycles (Stratton et al. 2008), control of the insect vector is generally seen as essential (Takken and Knols 2009).

Trends for malaria and other mosquito borne diseases are generally getting worse, although malaria has been a high profile and long standing issue in the international spotlight (discussed below). Dengue fever, however, is particularly attracting renewed attention (Gubler 2002), with range expansion and the general rise in fortunes of tropical nations (e.g. South East Asia) that are most threatened. Factors behind the resurgences include population growth, changes in demographics and land use, and the erosion of public health programs and institutions under fiscal austerity programs demanded by the International Monetary Fund and World Bank (Gubler 1998; Gubler 2002; Hay et al. 2004; Stratton et al. 2008). Increased and faster global movement of people and biological entities (e.g. livestock), and the consequences of a changing climate (Shope 1991; McMichael et al. 1996; Patz et al. 1996) have worked to increase the probability of rapid global spread of infectious agents, sometimes even before a disease is detected.

Box 4.2.1 – Poverty and infectious disease: a story in pictures.

Poverty and disease is increasingly recognised as being causatively related (see Appendix 2). Here is a simple juxtaposition of three maps to illustrate this relationship, including one of malaria transmission, which is something of a figurehead for insect DART research.



Map (A) shows a global map of poverty as derived from satellite data (Elvidge et al. 2009). **Map (B)** is a global rendering of WHO data on the burden of infectious and parasitic disease (in units of "disability-adjusted life years" (Lokal_Profil 2009). **Map (C)** displays a representation of the stability of malaria transmission (i.e. how 'reliable' or entrenched infectious processes are) across the globe (Kiszewski et al. 2004).

This increasing risk of mosquito borne disease is emerging at the same time (perhaps causatively linked in many ways) with a precipitous drop-off in the number and effectiveness of the tools we use to control both the vectors and the diseases (Takken and Knols 2009). Mosquitoes are increasing resistant to a wide array of insecticides (Hemingway et al. 2006). The malaria parasite, too, has evolved a succession of resistance to a succession of medicines (Hayton 2004), and recently the last chemical line of defence, artemisinin-based combination therapies, appears to have been breeched with the emergence of resistant strains in the Thai-Laos border region (Dondorp et al. 2009). Since there has been decades of disinvestment in such diseases of the poor, in drugs but also insecticides, we face years of lag time between new research into chemical strategies and their eventual approval for use (Trouiller et al. 2002; Hemingway et al. 2006; Takken and Knols 2009). There is an urgent need for new tools.

In the last few years, the entry of new and powerful players to the vectored disease control world have created a very different discourse and funding environment. On the one hand, the Bill and Melinda Gates foundation have initiated major funding programs to tackle malaria, and raised again the once-jaded notion of global eradication of malaria (see discussion in section 5.4, Appendix 2; see Box 4.2.2 for the difference between eradication, elimination and control). Biological DART strategies are now prominently on the agenda.

Box 4.2.2 – Eradication, elimination and control in infectious disease

Control
The disease no longer a significant clinical problem but its transmission continues.

Elimination
Transmission of the disease is interrupted at a national or regional level.

Eradication
Cessation of natural transmission of the disease across the globe. May refer to all or a subset of the disease-causing agents (e.g. one or several of the five human malaria parasites).

Adapted from Greenwood (2009).

Genetic control of insects is an idea with a substantial history, with a pedigree stretching back at least as far as the 1930s (Gould and Schliekelman 2004) – should a thorough genealogy of DARTs be written, a substantial chapter must cover this area. As clever and indeed as successful as some of these approaches were (below), inherent biology and limited understandings of genetic mechanisms placed restrictions on just how far such attempts could extend. In the past decade, a pathway to exceed these limits has opened up. Genetic transformation of an insect was first achieved in the early 1980s, with the use of the *P*-element transposon in that workhorse of genetics, *Drosophila melanogaster* (Spradling and Rubin 1982). There was a wave of optimism that such success could be quickly transferred to insect species of economic and medical relevance (Gould and Schliekelman 2004), but despite a sporadic handful of transformations across the years, reliable and transferable insect transformation systems only really emerged around the turn of the century (Handler 2001; O'Brochta 2003).

Genetic modification of insects is still not easy. It requires highly trained personnel and specialised laboratory equipment. Nevertheless, assuming the insect can be successfully (and securely) raised in laboratory, dedicated workers can now produce GM insects in a range of species, including mosquitoes. In addition, genome sequence information is increasing exponentially for all biology, and insect genetics is no exception. Several medically and agriculturally important insects have had their genomes sequenced and made publicly available, which greatly assists the design and analysis of GM strategies (Terenius et al. 2008). These trends have put vector control – and explicitly, malaria control – with GM technology high on the research and policy agendas of the global disease control community (Alphey et al. 2002).

Options for using insect transgenesis in insect and disease control generally fall into two basic strategies, population reduction or replacement (Terenius et al. 2008).

4.2.1 Population Reduction

This strategy uses genetic modification of the target insect to interfere with the population's ability to reproduce. This approach can involve the creation of conditionally sterile insects, insects capable of producing only one sex of progeny, or insects in which at least one sex carries a mutation that prevents mating in the wild. Conceptually, these approaches stem from the decades-old and well-demonstrated Sterile Insect Technique (Baumhover et al. 1955; Knipling 1955; Krafsur 1998). See Box 4.2.3 for particulars. In general, these strategies are thought to be self-limiting – the insects are designed to die out – and require an ongoing program to release the GM insects into the target area. The successful precedent set by radiation-based SIT interventions over the past few decades, without the use of chemicals and hence avoiding some of the worst environmental and health-related side effects of vector control programs, lends credibility to this strategy. The advent of widely-applicable genetic engineering tools for insects has opened the doors to a radical expansion of SIT, or variations (Catteruccia et al. 2009; Wilke et al. 2009; Alphey et al. 2010).

Genetically sterile insects (or their female-lethal variants) will likely be most applicable to local control and perhaps regional elimination campaigns against an insect vector and/or its disease. Only some of these strategies in fact qualify as DARTs: insects engineered to be sterile are, by definition, unable to reproduce. However, it is still worth considering them in this document because the techniques and institutions involved in their creation are the same, because they will in many cases be covered by the same legal frameworks, and indeed, they likely form the first release of transgenic insects for disease control and thus set an influential precedent.

Box 4.2.3 – The Sterile Insect Technique

The Sterile Insect Technique (SIT) was pioneered by Edward Knipling and Raymond Bushland in the middle of last century (Knipling 1955; Krafsur 1998), its success netting them the World Food Prize in 1992. At the time it was seen as one of the peaceful applications of nuclear energy, and as a consequence the International Atomic Energy Agency (IAEA) has taken a leading role in this technology (Schiff 1984). It runs a dedicated entomology unit, closely operating with the Insect Pest Control Section of the Joint FAO/IAEA Division of Nuclear Techniques in Food and Agriculture. This is one of the global centres of expertise in SIT, a repository of knowledge about the technique, and involved in the international (supra-governmental, i.e. UN-level) co-ordination of its application in many places around the world. Private enterprise has not, historically, been very involved in SIT provision, although that has begun to change (Quinlan and Larcher-Carvalho 2007). High-profile examples of SIT successes include the elimination of screw-worm flies in Libya (Lindquist et al. 1992) and North and Central America (Krafsur et al. 1987; with an ongoing program to halt reinvasion from the south). It is widely used at local and regional scales in agricultural areas for horticultural pests, (e.g. Mediterranean fruit fly, *Ceratis capitata*; Dyck et al. 2005).

The principle behind SIT is simple: release enough sterile males into a population such that the wild males are 'overflooded', and the subsequent generation will be greatly reduced. The technique can be devastatingly effective, and avoids the downsides of blunter instruments like habitat destruction (e.g. swamp drainage) or insecticides (with multiple non-target effects). It is not a simple system to establish, however. A large amount of expertise has been built up on industrial-scale (millions or billions per week) husbandry techniques, quality control, release rates and monitoring, the suitability of the insect as an SIT candidate, radiation regimes and the ability to sex-separate the animals pre-release. A careful balance must be reached between irradiation sufficient to reliably sterilise but not weaken the males, a balance sometimes unobtainable. Furthermore, reliably separating the sexes at industrial scales is essential, ideally in very early stages of development. Some species have, for example, size differences in eggs that enable mechanical sorting. For others, a mutation has been discovered that enables females to be killed in the final generation, for example using a heat shock treatment.

In many cases, no sexing mechanism or reliable sterilisation procedure has been found, and SIT cannot be applied. In the 1970s, SIT was twice attempted for mosquitoes, but was thwarted in Africa by war, and in India by popular protest due to perceptions the release was a genocidal plot (Dame et al. 2009). Technical factors and a lack of political will has meant that only recently has a radiation-based mosquito SIT been launched in Sudan (Dame et al. 2009; El Sayed et al. 2009).

The advent of widely-applicable genetic engineering tools for insects has opened the doors to a radical expansion of SIT, or variations (Catteruccia et al. 2009; Wilke et al. 2009; Alphey et al. 2010). The most prominent application of genetic modified insects is known by the trademarked name of Release of Insects carrying a Dominant Lethal (Alphey 2002). See text for details.

The most advanced (at least in terms of readiness to be deployed) of these sterility-based techniques is the proprietary technique, Release of Insects carrying a Dominant Lethal, (RIDL; Alphey and Andreasen 2002). A genetic mechanism suitable for the technique was announced within months of each other by two independent research groups independently, one in New Zealand (Heinrich and Scott 2000) and the other by the RIDL neologism's developers at Oxford University (Thomas et al. 2000). The technology has been most actively pursued by the Oxford team, and is now the basis of the spin-out company, Oxitec (discussed in detail in section 5.4). It should be noted, however, that there are other research teams around the world capable of producing genetically sterile insects for SIT programs, too, however (Gould and Schliekelman 2004).

There are, in fact, two versions of RIDL or RIDL-like strategies developed by Oxitec. The first operates almost identically to orthodox, radiation-based SIT, and is known as a bi-sex lethal. Using genetic switches derived from bacterial resistance mechanisms to an antibiotic[10], the inventors have devised a system such that the insects are bred to large numbers in captivity on feed containing tetracycline (Thomas et al. 2000). However, in the penultimate generation, tetracycline is removed from the feed, activating a lethal biochemical process in the insects. (Variations of the timing of the lethality – usually early in development to save costs in rearing – can be useful in the field, as the doomed larvae can in fact compete with wild-type larvae, adding an extra level of pressure on the target population). Oxitec has several species in which it has engineered its RIDL technique[11], including the dengue vector mosquito, *Aedes aegypti*. This particular product line, (a local variant developed in collaboration with the Malaysian Institute for Medical Research, OX513A-My), is about to be field-tested in Malaysia (Department of Biosafety Malaysia 2010). As an SIT-style strategy, it is not strictly a DART.

A variant on this technique, however, *is* competent to reproduce, and as such is indeed a DART. In this version of RIDL, the released males are able to produce offspring with wild females (Fu et al. 2007). However, in all the females of the resultant and subsequent generations, the killing mechanism will not be suppressed by tetracycline – female offspring will not reach adulthood. This will lead in turn to a proportional increase in males in the recipient population. That population will thus be reduced: immediately, by the lack of females (and with that, a reduction in bites and disease transmission, since only females bite), and; over time, by the lack of females with which to mate. Like the SIT, the female-killing version of RIDL is a strategy in population reduction, and the Oxitec platform is not the only instance that this sex-skewing strategy has been explored for insect control (Schliekelman and Gould 2000a; b; Schliekelman et al. 2005), or indeed solely within insects (e.g. in fish (Thresher and Bax 2003; Thresher et al. 2003; Thresher and Kuris 2004; Thresher 2007). Variants on the RIDL technique, however, include the use of a flightless female phenotype (Fu et al. 2010) – females that cannot fly can neither bite, nor engage in the courtship that leads to mating.

4.2.2 Population Replacement

An audacious alternative to the removal of an insect pest is the removal of a specific part of its nature – the part that causes problems for humans – without the species'

[10] This is the Tet On/Off system, owned by Clontech Laboratories, Inc., USA (Anon. 2007; Freundlieb 2007).
[11] See product listings on its website, http://www.oxitec.com.

or population's outright extermination. This is the concept of population replacement (Gould and Schliekelman 2004; Terenius et al. 2008). This approach envisages the genetic modification of the insect typically to render it incapable of carrying the disease agent, i.e. become "refractory". Other modifications are also plausible, including interference with the insect's ability to locate human hosts (Terenius et al. 2008). The idea of replacement has its origins in the 1940s work of the British biologist Frederic L. Vanderplank and Soviet geneticist Alexander S. Serebrovskii (Gould et al. 2006), but the explicit goal of genetically preventing insects vectoring disease was articulated at a 1991 WHO meeting in Tucson, Arizona (World Health Organisation 1991). The great difference between this and population reduction strategies is that, in this vision, the insect is maintained in the wild, continuing its ecological function – indeed, simply existing, not becoming extinct – but with an ostensibly minor[12] alteration to its nature, i.e. the ability to harbour a human disease.

Refractoriness has been pursued with great enthusiasm by the vector control and insect molecular biology communities (Alphey et al. 2002; Atkinson et al. 2010; Knols and Schayk 2010), but although several proof-of-concept systems have been demonstrated, human-relevant systems are lacking (e.g. blocked transmission of mouse malaria, but not human malaria), and it is unclear exactly how to drive such a modified genotype into the wild (Sinkins and Gould 2006; see Box 4.2.4). Nevertheless, many systems are being developed (Coutinho-Abreu et al. 2010), including reports of field-cage trials in Mexico by a Bill and Melinda Gates Foundation-funded consortium (Nightingale 2010).

While these techniques could be employed in what would strictly be considered local control programs, replacement of a population by these methods is more closely entangled with the idea of region-wide elimination of a disease-carrying genotype, or indeed a global eradication of a genotype that is capable of carrying the disease.

[12] The provisional nature of this claim, that the modification is ecologically negligible, is noted by the author, but also by at least part of the research community.

Box 4.2.4 – Genetic drive: an evolutionary process

Generally, a new gene will only spread throughout the species if it offers some advantage over those not carrying the trait (although there are exceptions to this). Many genetic modifications in a variety of species have proven to make life more difficult for the organism. The general expectation is that a GM insect will be less fit compared to its wild cousins and thus less successful in mating, *or* not particularly fitter and fewer in number, therefore likely to die out, disabling the disease controlling effect (Marrelli et al. 2006).

The goal here is a species- (or population-) wide introgression of the refractory gene: every mosquito should be genetically incapable of carrying the disease, permanently. All things being equal, (there are ways of trying to make sure this is not the case), the genetically modified mosquito – or at least the disease-resisting gene it carries – will require some assistance to push it out into the wild. This is referred to as 'genetic drive'.

Researchers have been working at this for some ten years or more now. Researchers have been exploring a range of complicated genetic 'tricks' to provide this drive. (Recent results suggest that in some cases, freeing the mosquito of the infectious agent may confer an advantage in itself (Marrelli et al. 2007; Scolari et al. 2010), but it is still unclear how effective or universal that may be). Drive strategies are difficult to explain without a detailed treatise on genetics. Many, however, involve a 'selfish' genetic element – a piece of DNA that has evolved in a parasitic mode to copy itself throughout a host genome without necessarily coming under the orchestrated control of the host's own genetic program or lending a physiological function (e.g. transposons, or homing endonucleases; Burt 2003; Sinkins and Gould 2006; Deredec et al. 2008). The insect genetics community is very familiar with many of these, as they form the basis of the genetic manipulation technology employed for insects (see text), and indeed the *P* element has been shown to have spread autonomously in *Drosophila melanogaster* populations the world over in only the last few decades (Anxolabehere et al. 1988).

Unlike viruses and germs, these genetic drive elements transmit only vertically. They do not, on their own, spread infectiously through the population*. This limits the rate of spread of the refractory transgene, as often only one copy will be passed on to a limited proportion of the progeny. Selfish genetic elements can multiply themselves from a single copy to several, greatly increasing the chances that that new recipient will pass on more copies to a greater proportion (up to 100%) of their own offspring. Linking a refractory gene to a selfish genetic element might therefore accelerate its spread throughout the wild.

Other approaches use selfish elements that impose a conditional cost in *not* having them. Some, like the *Medea* element (Chen et al. 2007; Marshall and Taylor 2009) will actually kill the embryos that have not inherited the element while inside the mother. Over time, these conditionally lethal dynamics may lead to all insects carrying copies of the *Medea* element, and the effect has been demonstrated in the lab (Chen et al. 2007). Similar dynamics, although at a different level, are seen in the intracellular commensal bacterium, *Wolbachia*, discussed in the text under 'Paratransgenesis and mutant symbionts'. Again, linking refractoriness to conditionally lethal elements like *Medea* would increase the efficiency of spreading a disease-resistant genotype into the wild.

* Horizontal transfer *does* occur (Daniels et al. 1990; Clark et al. 1994).

4.2.3 Paratransgensis and mutant symbionts

Refractoriness might also be achieved by the transformation of bacteria that normally live in or on the insect vector (viruses, too have been considered (Coutinho-Abreu et al. 2010). This is known as paratransgenesis. Microbes are generally much easier to transform than insects, although this approach would still need a mechanism to drive the engineered genotype into the wild. A related but non-GM approach is in the use of an intracellular symbiotic bacteria, a mutant strain of *Wolbachia* that has been introduced into the mosquito *Aedes aegypti* to reduce its ability to vector dengue, currently being considered for release in Australia and Vietnam (Jeffery et al. 2009; McMeniman et al. 2009; Moreira et al. 2009; Murphy et al. 2010). This bacteria has a drive mechanism (see Box 4.2.4) not dissimilar to some genetic drive elements with conditionally lethal inheritance. (See section 5.3.3 for the legal implications of its non-transgenic status). These strategies, with their proliferative and infectious properties, would likely be most useful in attempts at regional elimination and global eradication.

It is important to note before we conclude this section that the best opinion on the use of these insect DARTs envisages them not as single-shot solutions, but rather as a component of integrated vector management programs (Hero 2001; Knols et al. 2006; Knols et al. 2007; Yakob et al. 2008; Alphey et al. 2009; Beech et al. 2009b; Mumford et al. 2009; Takken and Knols 2009). Given the current failings and looming failures in insect vectored disease control, quite unlike immunocontraception, insect DARTs are destined to become more prominent in the near future.

5 Issues and implications for a research agenda

This section sets out a series of issues about DARTs that warrant further scholarly investigation. It draws on the two cases detailed above, and further, in an effort towards a generalised research agenda for DARTs. The structure is necessarily unevenly weighted, and length of the section is not a reliable indication of its relative importance.

5.1 Conceptual frameworks for DARTs

The concept of DARTs has been deployed here as a heuristic device. It has enabled the consideration of a previously disparate menagerie of technological ventures, made them distinct from other forms of technology and living processes, and revealed them as an interacting suite of phenomena that challenge the world in particular ways (see below).

As a heuristic device then, the idea of DARTs has some utility. However, the fact that the real-world examples of DARTs quickly recedes from mechanical objects to the interesting but categorically narrower field of biological control by transgenic and non-transgenic means suggests pragmatic schisms in the concept. Indeed, if heuristic utility is the objective, it might have been better to cast aside the technological speculations of the nano- and robo- researchers and simply focus on GM biocontrol. Nevertheless, even *if* non-biological technologies are not yet materialised, it is certainly wrong to say that it is a field devoid of effort. The past few decades has demonstrated the dramatic evolution of technological possibility. Who is to preclude the possibility of such things in the not-so-distant future?

It may be, therefore, that DARTs broadly conceived captures something essential. This is not a philosophical treatise, but it may be that the first recommendation of this review is to encourage a more analytically rigorous development and testing of the concept. This may be necessary and useful for increasing understanding and wisdom about governing technological artefacts equipped with such agency and an ability to populate. It may also be useful to understand the limits of DARTs, if only to understand the limits of claims about them and 'sibling' issues. These sibling issues include replication-incompetent devices that are quickly gaining sophistication, such as the use of kill-enabled robots in conflict (Singer 2009), replication-disabled biological devices like genetically modified forms of SIT (above), and indeed immaterial but nevertheless highly influential software agents in the digital world.

5.2 The task of mapping

Creating a comprehensive overview of DARTs, even within the subsection of GM biocontrol, is not a simple undertaking. Relevant programs exist as research concepts, simulation modelling exercises, proof-of-concept model systems in simplified environments, and indeed examples that are being put into the field today. The range of both the nature and the maturity of these projects make a census a challenging task, and there is no central forum in which announcements are made. In this respect, mapping DARTs resembles the challenges encountered in creating an overview of research and development in nanotechnology.

This trivial-sounding task will be an act of research in and of itself (see, for example, http://www.nanotechproject.org). For high-profile programs such as mosquito-based research, with researchers that are hosted in institutions that make publishing in the international peer-reviewed literature (in English) a priority, identifying the players and projects may be reasonably straightforward. The greatest problem may lie in adequately covering the diversity of proposals and ideas, and devising some coherent system of ranking between purely conjectural material on the one hand, and active research and development programs on the other. In addition, there is the interdisciplinary challenge of making sense of esoteric, complicated technological material and being able to chart the connections to points in the wider social matrix in which they operate, (of course, this is bread-and-butter to the ELSA/STS community).

However, the problem-solving nature of DARTs predisposes communication to occur within epistemic silos. Reviews of weed control using plant DARTs (Rector 2008; Hodgins et al. 2009; Rector 2009) may not be readily visible to DART communities working on insect or fish control, for example. Despite commonalities both conceptual and instrumental (e.g. cross-cutting simulation models that may be applicable to a range of species, and thus operating as a trading zone between disciplinary groupings), different epistemic communities may develop their own sites and terminology for discourse, the latter particularly making literature searches more difficult. As the New Zealand possum control work has demonstrated, DART development programs may be conducted by agencies that have a greater priority on internal communication (e.g. accountability to departmental lines of command) and/or publish late in the development phase, in national or regional journals that are not as visible to search engines as high-impact international journals. This issue may be compounded by language barriers. For example, a truly stunning amount of research effort in biotechnology generally is occurring in China, but this research is not always accessible to English-speakers.

There may indeed be several disincentives to widespread announcement of development programs. This author, for example, has attended discussions and reviewed research applications on DARTs that are covered by confidentiality contracts, and thus cannot be relayed. The rise of commercial approaches to research, stemming from wider moves in research funding policies around the world, but also from the particular vehicles that are employed to bring DARTs into operation, may introduce a greater level of commercial and strategic confidentiality. Traditional research institutions that host DART development may have policies that now demand the careful capture and exploitation of intellectual property (IP), for example. Philoanthrocapitalist organisations (e.g. the Gates Foundation) and technology start-ups (e.g. Oxitech) may be keen to both capture and leverage the value of their IP as quite fundamental matters of return on investment and generating revenue to survive or profit. In these cases, DARTs are developing in an environment in which there are many straightforwardly commercial reasons to avoid detailed or early publication.

Another interesting and problematic motive for confidentiality and careful 'information management' may be the need to maintain public goodwill. This may be acutely felt by philanthrocapitalist and start-up organisations – part of the rationale for establishing such structures is to escape constraints of larger and more established institutions. This increased freedom to operate is won at the expense of security of funding and tenuous legitimacy, a situation in which public goodwill attains a particular premium for their continued freedom to operate, or even to exist at all. Philanthrocapitalist organisations and social entrepreneurs recognise their vulnerability to campaigns from techno-sceptical voices, voices from organisations that may themselves draw on support from the same political constituencies. Anticipation of controversy, and ongoing competition for public support, may promote strategic silences from DART developers. Breeching this silence in the interests of public rights to know and the admittedly self-interested needs of an ELSA researcher may form a point of tension.

One of the challenges this task of discovery and collation brings is the manner in which it is to be made available. An easy answer might be the traditional model of publication. Books and papers are formats that the academic community is well-geared to produce, and universally recognised as valid outputs of research investment. Certainly, this has an undiminished value and should be expected and supported. However, relying solely on printed formats may be under exploiting the investment, and reducing the total value of such an exercise for a great variety of research communities and other actors. This is an important point in studying DARTs. DARTs are a wide-ranging phenomenon. They may, in future, encompass not only biological materials and entities, but also synthetic biological materials, devices of silicon, metal and plastic. The frame of reference might justifiably be made broader than this review to include virtual agents, especially if the linkages between cyberspace and devices in the physical world intensify, as many expect.

Despite the utility of forums provided by things like the Cartagena Protocol's Biosafety Clearing House, collections of works in journals that have taken an editorial line of interest (e.g. *Wildlife Research*), and the panglossian reach of the internet, lacunae remain. One of the most serious issues here is the potential for national interest considerations to lead to the wilful concealment of a DART to avoid diplomatic trouble. There are suggestions that exactly such covert actions happens in cyberwarfare already (Carr and Shepherd 2009; Korns 2009; Denning and Denning 2010). Practically, strategically and from a scholarly standpoint, notwithstanding the limits implied by the integrity of the concept of DARTs (above), it may be worthwhile to establish a dedicated research effort to list DARTs in their various forms and manifestations.

5.3 Law and international relations

Unsurprisingly, there is no overarching legal framework that is readily apparent to meet all the challenges posed by DARTs, at any level – national, sub- or supra-national. In fact, although DARTs may be philosophically regarded as similar – not a given in itself (above) – a unified legal instrument may not at all be appropriate. It can be expected that the domains of application and possible consequences of emerging biological DARTs on the one hand, and promised-but-not-yet-materialised mechanical DARTs on the other are rather different. It is therefore likely that these would call for different legislation, binding very different actors and with an eye to different adversities and risks. Indeed, there are already a range of legal instruments that will have bearing on DARTs, even if they have not yet been deployed in the real world. These are important, even if they are incomplete in dealing with the particular challenges of DARTs (below).

Workable principles established in one domain may be useful in informing the construction of another. Liability regimes in particular, based on the moral implications of releasing active agents that will operate and proliferate without further instruction from their makers/releasers, may be highly transferable. As society develops its own set of norms about these objects, there may be a public demand for a uniform code of conduct to be applied, even if that may be maintained under different pieces of legislation. What may inform that normative construction sociologically is a question for dedicated research, and perhaps intervention in the vein of the public participation work done in the more politically active forms of scholarship.

5.3.1 International issues and regulatory network

The greatest regulatory challenge posed by DARTs is their ability to move out from the area for which they have been approved, and establish there. While escape from regions within a nation and invasion of surrounding sub-national jurisdictions may be problematic (e.g. from a national park into agricultural lands), national courts and legislature already in place offer an avenue to resolution. Either through specific preventative regulation, or civil liability regimes and the self-interest in avoiding lawsuits, the existence of these legal pathways instils a proactive restraint of dangerous DART releases. However, legal liability is difficult to establish when dealing with transgression of national borders – in international law, there is often no ultimate supra-national legal authority that can mediate dispute. DARTs are particularly prone to international disagreements because nations tend to represent a level of organisation under which attitudes to a) a particular species (pest or prized possession; Henderson and Murphy 2007), and b) particular technological platforms (e.g. genetic manipulation) may be unified, in policy if not in fact. The problem can be simply illustrated with two scenarios: one, in which the DART crosses a border and causes an effect that is unwelcome, and; two, in which a DART crosses a border and its unauthorised presence – for example, it's genetically modified nature – forms the core of dispute, (although its function *per se* may not be objectionable).

We have already examined one case exemplifying the first scenario. Generally speaking, Australia wants its possums (and related species) but New Zealand doesn't. Given the properties of the possum-control nematode DART (in as far as it could be predicted from its design), it is not hard to imagine infectious material, either in accidentally imported soil on a machine or hiking boot, or intentionally smuggled, getting into Australia (Gilna et al. 2005). There is precedent: in 1997, rabbit viral hemorrhagic disease was detected in New Zealand, presumed to have been smuggled in from Australia as a pest control agent against rabbits despite government intentions to the contrary (Parkes et al. 2002). Even perfect, but probably infeasible, quarantine restrictions (Tyndale-Biscoe 1997) would probably fail to exclude a GM *P. trichosuri* (Gilna et al. 2005).

Another example of the same scenario is the conflict of interest between two separate programs to develop viral DARTs targeting rabbits in Spain and Australia (see Box 4.1). Spain seeks to increase rabbit numbers, which are socially (hunting, culinary) and ecologically important. It has created a GM rabbit virus that is infectious, but rather than sicken the animals, instead vaccinates them against two diseases that are devastating their numbers (Bárcena et al. 2000; Torres et al. 2001; Angulo and Barcena 2007). On the other side of the globe, Australia has used those very same diseases to reduce invasive rabbit populations (which seriously damage agriculture and biodiversity); and furthermore was attempting to genetically engineer the same virus to improve rabbit control (Fenner 2000; Van Leeuwen and Kerr 2007; Henzell et al. 2008). Clearly, the objectives of these DART projects were diametrically opposed (Angulo and Cooke 2002; Angulo and Barcena 2007; Angulo and Gilna 2008b).

The use of GM mosquitoes for disease control offers a plausible example of the second scenario. Generally speaking, *nobody* wants these diseases. On the other hand, not everyone will be happy to have GM insects buzzing around their homes and environment, however, and certainly not without formal processes of approval (Knols et al. 2006; Knols et al. 2007; Angulo and Gilna 2008a). This is especially concerning in disease control, where disease-endemic regions comprised of many nations may well have to co-ordinate integrated control measures – a potentially tricky job in itself – of which a DART may be but one element in an multi-pronged integrated vector management strategy. Would the objections of one nation in such a cluster be of great enough concern to preclude the use of DARTs in the others? Conversely, what if one nation felt the need and the right to pursue a DART to solve their pressing disease problem, (or any other, for that matter)? Would they be constrained? The Right of Sovereignty, a founding principle of international law, recognises the right of nations to govern their own affairs without the interference of others (James 1986; Scrutton 1996). What would be the mechanism of resolution of such a dispute? Quiet bilateral or multilateral negotiations may be the first port of call (as may have been the case between Australia and New Zealand over possum control; Henderson and Murphy 2007), but existing international agreements and treaties will quickly move to the fore in protracted disputes, and will likely frame expectations of negotiations right at the beginning, regardless of the forum. However, which element of the extant network of laws and treaties that applies to DARTs foremost is not entirely clear.

One of the looming challenges in identifying a regulatory network that applies clearly and unambiguously to biological DARTs – at least those that we have surveyed here – is that they have multiple identities: they are biocontrol agents, they are (often) genetically modified species, they are (often) members of recognised pest or pathogenic species, and they are designed to be (or are well-equipped to become) invasive (alien) species. While the overlap between these categories is easy to see, and has been recognised in public and scholarly debate for some time (e.g. Nentwig et al. 2007), each nevertheless falls under a different regulatory regime. This is true at an international level, but may also be played out at national levels as well. Understanding how these different instruments interact, the relative priorities that are assigned to them – especially in the case of conflict between definitions and provisions, and in forums for dispute resolution – and the full scope of the resulting coverage they provide represents a considerable challenge, and one that is not purely soluble by the action of scholarship. Ambiguities in law are often only resolved by decision-making in real cases, not *a priori*, and at an international level, negotiation between state actors is essential.

These caveats notwithstanding, a careful mapping out of the regulatory network that is applicable to DARTs – perhaps from legally qualified personnel – is one of the clearest needs identified in this report. Ancillary to this is an investigation of the ways in which, in the early history of DARTs so far as well as in up-coming applications, international relations are accommodating these highly mobile and potentially contentious objects.

5.3.2 The Cartagena Protocol on Biosafety

For genetic modification, the primary instrument is the Cartagena Protocol on Biosafety, which was established as an instrument of the Convention on Biological Diversity (CBD or Convention). The Protocol is an instrument of the CBD (1992), attempting to clarify the international institutional arrangements dealing with the products of modern biotechnology. The negotiations that created the Protocol stemmed directly from Article 19(3) of the Convention (Mackenzie et al. 2003):

"The Parties shall consider the need for and modalities of a protocol setting out appropriate procedures, including, in particular, advance informed agreement, in the field of the safe transfer, handling and use of any living modified organism resulting from biotechnology that may have adverse effect on the conservation and sustainable use of biological diversity."

The Protocol falls short, however, in adequate provisions for the challenges of DARTs (Angulo and Gilna 2008b). Its provisions are heavily reliant on the concept of a "living modified organism" (equivalent, for our purposes, to a GMO) that will not move on its own accord, providing ample opportunity for regulated and human-facilitated transport across borders. By their very design, DARTs do not offer this luxury of control (Gilna et al. 2005; Knols et al. 2006; Henderson and Murphy 2007; Angulo and Gilna 2008b; Angulo and Gilna 2008a; Marshall 2010). Even GM crops may cross borders independently (Bagavathiannan and Van Acker 2009; Nickson and Raybould 2009). The Protocol's provision for Advance Informed Agreement, under which no environmental release would be approved in a nation when there is reasonable risk of its unauthorised movement across the boundary of another without its consent, would seem to preclude the deployment of any DART except in that handful of cases in which bi- or multilateral agreement could be obtained. As we have seen in the case of New Zealand's possum control DART, and again in Australia and Spain's conflicting objectives for their viral DARTs targeted at rabbits (see Box 4.1), a significant amount of time and money can be invested in DART development – even when conflicts are obvious and openly discussed – without seeking agreement (Angulo 2001; Angulo and Cooke 2002; Henzell 2002; Angulo and Barcena 2007; Henderson and Murphy 2007; Angulo and Gilna 2008b). In the case of the Spanish rabbit-protective DART, limited environmental release has already occurred as part of field-testing (Torres et al. 2001; Angulo and Barcena 2007).

In a recent move, an Ad Hoc Technical Expert Group (AHTEG) under the Protocol has published guidelines for the risk assessment of GM mosquitoes (Ad Hoc Technical Expert Group on Risk Assessment and Risk Management 2010). As useful as that document may be – and it is still untested – the conduct of a risk assessment, however adequate, will not substitute for guidance on GMOs that are designed to disperse into the environment and propagate, i.e. a DART. As such, the Protocol now is best equipped to offer guidance for the use of non-*intentionally*-proliferating GMOs, like the genetic approaches to the Sterile Insect Technique (reviewed in 4.2), and where small regional groupings of nations from which such a non-proliferating biocontrol GMO may not be expected to escape can establish multilateral agreements (Marshall 2010). Genetic drive mechanisms, on the other hand, have a global scope, demonstrated by the rapid spread of the *P* element through all of the world's populations of *Drosophila melanogaster* (see Box 4.2.4 on genetic drive; Marshall 2010). Global agreement on the use of GM technology like this, even when targeted against some of the worst ills of humanity, seems ambitious if not impossible. Where national objectives for the target organism are implacably opposed, only in the most favourable of political circumstances – and quite possibly, therefore, a condition of environmental negligence in one nation, at odds with the widely supported CBD – could a permissive arrangement be established, at least for DARTs in which the aim is to reduce or eliminate the target species.

These matters are complex enough when considering the extremes of cases: deadly diseases, species elimination, protected species and declared pests. More subtle actions of DARTs, in which their administration is in fact an attempt to modulate the properties of the wild population without their extermination – like population replacement in insect vectors – are a greyer zone. Is that modulation acceptable? To whom? Under what definition? Legal instruments like the Protocol and its parent, the CBD, frame their concerns around generally poorly-defined notions of environmental damage and harm (Bartz et al. 2010). Even in cases in which a species is suggested for outright removal, such as mosquitoes, it seems that even prominent scientific journals like *Nature* can mobilise scientific opinion to suggest it is an ecological negligible event (Fang 2010). Are we lined up for another round of 'sound science' disputes (Levidow 1999; 2000)?

In short, the Cartagena Protocol has serious deficiencies for regulating DARTs. The regulated cross-border flows of living modified organisms (as envisaged in an ideal performance of GM crops and their products) in which autonomous mobility may be feasibly contained does not apply here. Given the highly constrained negotiating space available to the Protocol, an auxiliary instrument may be difficult to obtain. Further, given Australia's pioneering role in DARTs, the United State's technological capacity and disposition, a modification to a protocol to which these nations do not and are unlikely to subscribe seems of little use. Entangling DARTs with regulation of commodity trade any further than it already must (e.g. control of agricultural pests Williams 2007) will probably result in poor biosafety outcomes. It seems timely for the development of a new protocol specifically designed for DARTs (Angulo and Gilna 2008b; Marshall and Taylor 2009). Dedicated research to this end is needed. As daunting as the prospect of yet another treaty on biotechnology may be, a specific treaty on biological DARTs offers another advantage, namely the inclusion of DARTs that do fall under existing definitions of modification, (discussed next).

5.3.3 More than "transgenics"

Despite the shortcomings, the widely supported (if poorly implemented) CBD views the Cartagena Protocol to be the sole instrument it uses to regulate GMOs, and a great many nations have enacted national legislation that follow its stipulations. It is worth noting, however, that the sign-up to the Protocol is not universal. Australia and the USA are notable exceptions in this context. These nations have taken different approaches to the regulation of GMOs. In the US, regulatory oversight is distributed sectorally across organisations like the Environmental Protection Agency, the Department of Agriculture and the Food and Drug Administration. Regulation in the US does not rely on the transgenic nature of the organism to trigger oversight, (based on the principle of substantial equivalence). When one considers the criticism that is often levelled at that approach from nations and actors that are more wary of transgenics *per se*, it is ironic that this arrangement may in some ways be more suited to DARTs than frameworks that rely on the molecular *in vitro* techniques as a regulatory trigger.

In Australia, by contrast, the national regulatory regime covers transgenic organisms reasonably well, but specifically excludes "intragenic" organisms (Russell and Sparrow 2008). Intragenic organisms are those produced by genetic modification of their own genetic material, as opposed to transgenic organisms, in which the "trans-" denotes the presence of genetic material from another species (Nielsen 2003). This distinction is highly relevant to DARTs. Australian researchers have been now spent several years developing a "daughterless carp", meant to act as a population reduction strategy for invasive European carp (*Cyprinus carpio*; Thresher and Bax 2003; Thresher 2007; Saunders et al. 2010). The key to the technology is a genetic modification solely of the carp's *own* sequences that causes females to develop as males, a heritable condition – population reduction would be achieved by the gradual elimination of females in the wild. Daughterless carp then, are intragenic, and while they may indeed be classifiable as a "living modified organism" under the Cartagena Protocol, they nevertheless sit outside the coverage of non-signatory Australia's national GMO biosafety legislation.

The daughterless concept has been demonstrated in the laboratory, and at a recent meeting on invasive fish control in Minneapolis, USA in June 2010[13], a significant amount of interest was expressed in the prospects for using it in other species. The technique has been considered also for other invasive species in Australia, such as the highly problematic cane toad, (*Bufo marinus*; Hazell et al. 2003; Thresher 2007; Abramyan et al. 2009; Saunders et al. 2010). In Australia, and conceivably in other jurisdictions where national legislation is framed in terms of "transgenics" specifically, this DART sits outside of legislation intended to be the sole governing instrument for GMOs, and with that exclusion, is exempt from the mandated risk assessment and biosafety requirements of the act. This is a serious failing. (It should be noted however that in Australia, the host institution and its inventors have expressed a view that the technology should indeed come under a process of regulatory oversight, e.g. Hirsch 2005; Fulton and Grewe 2010).

This is not the only instance in which a DART falls outside legislation for GMOs. Australia again is host to a research program that has established a non-transgenic DART, this time for the control of dengue-carrying mosquitoes (discussed briefly in

1 [13] *International Symposium on Genetic Biocontrol of Invasive Fish* (Anon. 2010b). The author, BG, attended.

section 4.2.3). The technique employs a mutant strain of the symbiotic bacterium, *Wolbachia*, that reduces the mosquito's ability to host and transmit the disease (McMeniman et al. 2009; Moreira et al. 2009). It is currently being considered for release in Australia and Vietnam, and to this end, a risk assessment has been commissioned and published (Murphy et al. 2010), to be used in discussion with the authorities, although exactly under what legislation is unclear. This mutant has not been derived by techniques of genetic modification, neither by Australian or the Protocol's definition of a living modified organism – it is a serendipitous mutant discovered in a laboratory (O'Neill 2009; Marshall 2010). Yet, the properties of this mutant are decisively invasive, and are part of what makes the DART strategically valuable. In the biocontrol of fish, too, there are several strategies in which genetic – but not genetically modified – techniques can be used to construct DARTs[14]. A good example is the notion of a Trojan sex chromosome, in which fish are manipulated at gametic and embryonic stages by hydrostatic pressure and hormones to be genetically 'super-male' (i.e. two Y chromosomes), but physiologically female: the sex ratio of subsequent generations will be heavily biased towards males, thus reducing the reproductive capacity of the population as a whole (Gutierrez and Teem 2006; Cotton and Wedekind 2007). Discussions at the Minneapolis fish biocontrol workshop (Anon. 2010b) revealed just how patchwork legislation is even within the US, and reflected across the North American continent and further afield. Clarification of the relevant regulations is highly desired by both innovators and managers.

Genetic modification, in the manner in which public and legal frameworks alike have come to understand, may not be a sufficient regulatory trigger to ensure biosafety. This insight applies not only to DARTs, but also to advances in crop science, in which the use of systematic mutations and sophisticated genetic mapping are producing highly novel phenotypes – in many ways, equivalently radical to those induced by transgenesis – without genetic engineering as it is understood today (Babu et al. 2003; Shivrain et al. 2007; Rommens 2008; Breyer et al. 2009; Thomson et al. 2010). There are emerging suggestions that, within food and biosafety legislation, regulatory scope should be rationally expanded to encompass these bioinnovations (Morris and Spillane 2008; Devos et al. 2010; Kuiper and Davies 2010; König et al. 2010). Should that happen, DARTs should be considered, too.

5.3.4 Species declared as "pest" or "endangered"

It is no accident that DARTs are being considered for use so extensively in the control of invasive (pest) species. Their utility lies in ability to reproduce and disseminate themselves into the very environment that is occupied by the pest, often as a modification of the pest organism itself. In effect, and sometimes by legal definition within nations, DARTs themselves may be invasive species. For researchers and would-be users of the modified pest, this is not a trivial point. Invasive species are often subject to legal sanction – declared a pest, it can be illegal to keep, transport or release these organisms in such a jurisdiction. One of the advantages of *P. trichosuri* as a DART candidate was that researchers discovered they could by-pass the regulation-heavy "pest" possum and use the sugar glider as a laboratory host, instead (Nolan et al. 2007).

Should DARTs created from officially declared pests, special legislation or special exemption will be required before they are actually released. This is both

[14] and sterile 'DART-like' fish, *sensu* bi-sex RIDL in insects (Box 4.2.3).

problematic, as a source of uncertainty for all actors in the field, but also a source of opportunity to design a regulatory framework that is appropriate to the special challenges these DARTs may embody. Presumably, since this is a problem of legislation at the national level, the issue is important but tractable. International agreements that specify pathogens as restricted materials, either of humans or other species, and treaties that cover endangered species and their transport (e.g. the Convention on International Trade in Endangered Species) may require special attention for some DARTs, since their negotiated multi-state nature may make decision-making a less-than-streamlined process.

5.3.5 DARTs as invasive species

Regardless of a transgenic nature or otherwise, DARTs may be considered invasive species in themselves. Within nations (and multinational groupings like the European Union – here referred to under the term "nation" unless otherwise specified), restrictions and management actions may be imposed under existing legislation, but this is not a given. The regulation of invasive species is well developed in some nations but poorly considered in others, struggling even to be seen as a priority for enforcement at all (Miller and Fabian 2004). As the impact of invasive species is starting to be quantified, particularly in financial terms (McLeod 2004; Pimentel et al. 2005; Hulme et al. 2009a), and in frighteningly large numbers, the issue is gaining prominence. Currently in Europe, there is a flush of reports in scientific journals like *Science* and others (Hulme et al. 2009a; Hulme et al. 2009b), and the popular press (Dannenberg 2010; Monbiot 2010). A messy and poorly enforced (or enforceable) network of international instruments does exist, generally divided into sectoral concerns such as biodiversity (e.g. the CBD), animal health, (e.g. non-binding Codes administered by the World Organisation for Animal Health, the OIE) and crops and weeds (e.g. the International Plant Protection Convention, the IPPC; Shine 2007). While attempts are being made to improve co-ordination between these instruments, progress is slow, particularly given the implications a serious approach to prevention of invasive species may have for commerce. Developments in this area will have direct implications for DARTs, and conversely, consideration of DARTs needs to be on the agenda for the establishment of any formal regime.

5.3.6 DARTs as pathogens

As distinct from invasive species, some DARTs may in fact be considered pathogens threatening biodiversity and, importantly, agriculture[15]. In stark contrast to international regimes designed to protect biodiversity, there is a well-established regime to handle threats to economic assets like crops and livestock. The terms of membership to the World Trade Organisation (WTO) clearly allow for the imposition of sanctions when there is a scientifically credible threat to agriculture (and other biodiversity, albeit rarely invoked; Maruyama 1998). Given the WTO's influence, it would be an important forum to mediate disputes that may arise from the imposition of biosecurity-based trade restrictions (WTO 2005). In the case of a DART targeted at animals, this would involve a formal response from the OIE, who would inform the WTO under an existing arrangement (Sendashonga et al. 2005). We are still awaiting a formal policy to be issued from the OIE on animal pathogens used to address wildlife, although some authors suggest they are opposed (Henderson and Murphy

[15] Creation of DARTs from human pathogens has not been visibly or credibly been discussed, and would sit rather firmly within the domain of biosecurity and weaponry. I exclude its consideration from this report.

2007). The IPPC is the equivalent accredited reference organisation for threats to plant health, and has constructed detailed guidance pertaining to phytosantation that will have a bearing on the governance of DARTS. Explicit prohibitions of activities are usually avoided under this regulatory network (Secretariat of the CBD 2001).

The IPPC publishes internationally recognised standards relating to plant health, including the International Standards for Phytosanitary Measures (ISPMs), under the authority of the FAO. ISPM 3, *Guidelines for the Export, Shipment, Import and Release of Biological Control Agents and other Beneficial Organisms*, lays out non-binding but influential guidelines for biocontrol agents (International Plant Protection Convention 2005). The North American Plant Protection Organisation (NAPPO) has also produced a range of influential documents and guidelines that will have direct relevance to DARTs in North America, and by virtue of geopolitical influence, beyond. In particular, NAPPO established a framework for the use of transgenic arthropods in biocontrol (North American Plant Protection Organisation 2007). In general, biocontrol regulation is relatively well-developed in Australia, New Zealand, Canada and the USA, but other jurisdictions lag in their legislative oversight in this area (Hunt et al. 2008). There is no international instrument governing their use, although the threat of trade sanctions under WTO rules must surely exert an informal governance on the practise.

5.3.7 Liability and redress for DARTs

Liability forms perhaps the most important regulating driver in the DART legal landscape. This is the engine that – within the bounds of diplomatic action – drives considered constraint in the use of DARTs to pursue national interest. Although its coverage is incomplete, the Cartagena Protocol has just established a long-overdue regime for Liability and Redress. Coverage of the agreement is currently scant, but indications are that it will operate on an administrative basis as opposed to civil liability[16]. Nations may enact national-level regimes under which injured parties may seek damages, but it seems that the emphasis will be on corrective and restorative action. Exactly what those actions might be, given the nature of DARTs we have explored, and indeed what if anything could be done in the event of inadvertent transfer (Gilna et al. 2005; Angulo and Gilna 2008b) are unclear. As an added complication, since the fundamental properties of a DART (transgenic or otherwise) includes the capacity to reproduce, and errors in the reproductive process will lead to evolutionary changes, the nature of a DART will change over time. How liability regimes will handle damage incurred from DARTs that have evolved to something substantially different from their original design is an open and thorny question. The difficulty in defining “harm” and “damage”, especially in an environmental context (Bartz et al. 2010), only deepens the problem.

5.4 Political legitimacy and norms

While legal questions, incompletely sketched in the preceding, demand a considerable amount of scholarly and policy attention, there are a raft of political and social issues that are raised and revealed by DARTs. This is a survey of some of the most obvious.

[16] I draw here on an e-mail newsletter from the Third World Network, Malaysia, whose members formed part of the negotiations over this provision.

5.4.1 Destabilisation of existing regulation of biologicals

While the challenges for establishing an adequate regulatory regime for DARTs are substantial, there lies in these negotiations a hidden threat. It is not impossible to imagine that the consensuses hard-fought-and-won over components of DART issues (e.g. GM regulation) may be destabilised by both the material effects of DARTs themselves and by the weight of logic behind the fundamental unity of GMOs, novel (non-transgenic) biocontrol agents, unmodified biocontrol agents, introductions of species for other uses (e.g. stocking for economic purposes, like the king crab in Norwegian waters; Wessel 2004; Jørgensen and Primicerio 2007), and biosecurity issues. Previous resolutions often, like as not, rely on a lack of enforcement of existing agreements. Biodiversity has been the most obvious shock-absorber under this dynamic. The vague language of the CBD facilitates wide sign-up but poor operationalisation of its precepts (e.g. in invasive species management; Shine 2007), often failing to convince decision-makers of the priority of biodiversity conservation when confronted with large, numerate valuations of the unrestricted trade it may threaten. The increasing recognition of the economic value of biodiversity as ecosystem services (Costanza et al. 1998), and the economic damage wrought by invasive species (McLeod 2004; Pimentel et al. 2005; Hulme et al. 2009a) work to remove this political shock-absorber. The issue of regulation, its co-ordination and the gaps may soon be forced into the spotlight even without DARTs.

As an example of potential DARTs disruptive potential, consider the Cartagena Protocol. The negotiations on the Protocol were far from easy, and after almost complete collapse, required an "extraordinary Conference of the Parties" to finalise the text (Newell and Mackenzie 2000). Records of these negotiations (Secretariat of the CBD 2003), show a strong preoccupation with agricultural applications of biotech and their trade. Several coalitions of nations emerged during the negotiations, including the Miami Group (Argentina, Australia, Canada, Chile, Uruguay and the USA), a name often colloquially interchanged for "the exporting countries" (Falkner 2000), and the European Union, well-known for its very cautious approach to GM foods (Mackenzie et al. 2003). The introduction to the Protocol reads as follows:

> "[The Protocol]… provides an international regulatory framework to reconcile the respective needs of trade and environmental protection with respect to a rapidly growing global industry, the biotechnology industry."

The result was a protocol that appears to be tailored to the needs of international trade of agricultural GMOs (however contested that arrangement may in fact be), with other GM applications as peripheral although not insignificant concerns. Nevertheless, the Protocol applies to many DARTs as well, which share many characteristics of invasive species. The Protocol's parent, the CBD addresses invasive alien species, (poorly), which theoretically covers any invasive GMOs, but its signatory nations view the Protocol as the prime instrument for GMO regulation. A variety of international organisations (including the CBD Secretariat) recognise that GMOs may indeed be invasive in some circumstances (Secretariat of the CBD 2001; Arriagada Rios 2005; OIE 2005; Sendashonga et al. 2005), but they have been in some ways kept separate.

The establishment of the Protocol was an enormous achievement, and represents a significant fraction of expenditure of the world's "political capital". Even fulfilment of outstanding elements, whose later negotiation was agreed to but incomplete at the time of signing, like Liability and Redress, have resulted in extraordinary sessions and came close to collapse. A significant bloc of nations remain outside the Protocol, several of whom are highly active in DART research. It may be worth avoiding exacerbating an already fraught situation, in which agriculture commodities exert such a strategically structural influence, and establish a separate protocol for their governance (Angulo and Gilna 2008b; Marshall 2010).

5.4.2 Legitimacy – limits and excesses

While DARTs are clearly technological solutions that encompass a lot of uncertainty and obvious plausible risk, they are still imagined and pursued. How is this so? Part of the answer lies in the legitimacy gained from the seriousness of the problem to which they are targeted. Tracking the limits of this legitimacy, and noting where and why the DART imaginary exceeds that license, is a clear research priority. In the two cases we have examined, we see two different scales and magnitudes of problem, impacting very different actors and values.

Possums are estimated to cover over 98% of New Zealand, and have had a devastating impact on the unique ecology of New Zealand (which is very different from Australia's) through habitat destruction, competition and direct predation (Cowan 1990). Possums are a host to bovine tuberculosis, and so are a major threat to the nationally important agricultural sector (dairy and beef, but also farmed deer), with a 1990 estimated risk of $NZ 2 500 million in sanitary trade barriers (Cowan 1990). Surveys now find >90% of New Zealanders recognise possums as a problem, with both environmental and economical concerns prominent in focus group responses (Wilkinson and Fitzgerald 2006). A New Zealand National Science Strategy Committee (NSSC) constituted in 1992 established "clear research priorities for biological control" of possums (Anon. year unknown). Biological control was nominated as the only cost effective solution (Heath et al. 1994), contrasted with traditional methods that "are expensive, and cannot eliminate the problem"[17]. The goal was nothing less than a "'permanent' solution", (quotation marks in original) with the "spectacular advances in molecular biology… to develop techniques for solving pest problems" clearly in the spotlight (Atkinson and Wright 1993).

Almost two decades later, that resolute determination to develop a bold permanent solution was dead. After highly visible and widely recognised criticism of the project (Newby 2003; Gilna et al. 2005; Henderson and Murphy 2007), governance of this DART seems to have been so problematic that it was better for the New Zealand authorities not to allow the device to be brought to term (Weihong 2009). This "null result" is in some ways just as important as might be the establishment of framework to deploy it. It points to the deep and intractable conflicts that a DART, conceived in the best of intentions and expectations within one particular jurisdiction (and environment), may generate when the prospects of its unauthorised spread are imagined as credible enough to be taken seriously. Here, there is indication that expectations of protest, within New Zealand and beyond, telegraphed the consequences of deployment from beyond the fuzzy boundary of the future, and were received as ugly enough and substantive enough to cancel the research before a prototype had been developed. It is worth emphasising, however, the context in

[17] Note the lurking and recurrent trope of elimination – a final solution that would eliminate the beast once and for all. It pops up frequently, but is equally often retreated from, and restated much more rationally (scientifically and economically) as a reduction of possum numbers (or occasionally as a reduction of tuberculosis-infected possums) beneath a threshold under which they do negligible harm.

which this political calculus was performed. The New Zealand DART was conceived of as a “permanent solution” to an ongoing threat to budgets, wildlife and industry. As important as these assets are in neoliberalised Western societies, there are limits to the legitimation they can lend to projects and initiatives.

In particular, we can note that there are existing alternatives to possum control with a DART, proven and currently practised, and that human health and bodily wellbeing are not threatened by the possum menace. Were possums to be predating humans – creeping into babies cribs in the dead of night, for example – locking them into lives of fear and mortal uncertainty, we might expect the outcome to have been very different. Mosquitoes and disease, however, offer just that scenario.

Successful elimination programs and rising standards of living in the last century mean that the memory of malaria has all but faded from the minds of the global North. In contrast, gains made in poorer nations have steadily eroded to a situation in which an estimated 2 billion more people are susceptible to malarial infection today (Hay et al. 2004). Malaria is currently endemic in 109 countries, a combined population of 3.3 billion people, with sub-Saharan Africa being the worst afflicted (World Health Organization 2008). WHO reports 247 million cases of malaria in 2006 alone, with around 1 million fatalities (World Health Organization 2008). Most mortality occurs in children; malaria is responsible for about 25% of deaths in children under five in areas most severely affected by the disease (Snow et al. 1999). Appendix 2 gives information in more detail.

Tackling diseases like malaria is increasingly seen as part of an attack on global poverty (Box 4.2.1; Gallup and Sachs 2001; Sachs and Malaney 2002; Bonds et al. 2009). Combating the ‘diseases of the poor’ has become enlightened self-interest for the global North, as globalisation and climate change have raised the possibility of tropical disease and their vectors invading richer, cooler latitudes (e.g. Feresin 2007; Lines 2007; Rosenthal 2007).

However, trends are generally getting worse. Dengue fever particularly is attracting renewed attention (Gubler 2002). Factors behind the resurgences include demographic and socio-economic factors, including emerging centres of wealth and commerce in Asia. They also include major failings by the institutions, policies and demands of the North, e.g. the International Monetary Fund and World Bank (Gubler 1998; Gubler 2002; Hay et al. 2004; Stratton et al. 2008).

Over the last 60 to 70 years, at least two programs of malaria control advanced by supranational organisations like the WHO have been high-profile failures, characterised by confusion, under-resourcing and broken promises (Narasimhan and Attaran 2003; Yamey 2004; Tanner and Savigny 2008; Greenwood 2009). (It is no accident that economically blossoming Malaysia, threatened now by dengue, yellow fever, and other viruses, is stepping up to take a pioneering role in RIDL-based dengue control). By the early years of this century, expectations of success over diseases like malaria were rather modest. Diseases of the poor had assumed the identity of slow motion tsunamis that were simply normal, daily disasters.

Despite this gloom, the world was surprised to discover that, in small malaria endemic states like Zanzibar other regions, concerted efforts (focusing on mothers and infants, prophylaxis and benetting) managed to reduce malaria incidence by up to half (UNICEF and Roll Back Malaria Partnership 2007). This inspiring and but incomplete accomplishment was proof that inroads could in fact be made against an "intractable" disease. It became fundamental in spurring – or perhaps validating – a new surge of optimism.

Riding on that crest came a second event. At a conference in Seattle in October 2007, under the spotlight of the world, Melinda Gates declared that the world should refocus and envision a world in which malaria was eradicated. Among the battle-weary of the public health community there was a moment of polite-but-embarrassed silence. Nevertheless, the audacious goal was quickly reaffirmed by none less than the WHO and the Roll Back Malaria campaign (Greenwood 2009).

This is an interesting constellation. New and globally powerful actors – powerful in social dimensions perhaps like aristocracy in previous ages, but powerful in material/technological dimensions in unprecedented ways – have staked a claim in an issue that invokes compassion and justice for underprivileged humans. The targets, an uncharismatic set of insects and diseases, are not well regarded around the world, although those mindful of ecological function (and perhaps ecocentric philosophies) may not be so sanguine at their vilification. And, in resonance with the rhetoric of neoliberal conservatism, state and supra-national agencies have demonstrably failed.

On many lines of accountability, then, DARTs to tackle human diseases carried by mosquitoes have widespread alignment with the dominant values of the day, and unlike possums and Australia, have no clear champion to protect them, and certainly not with manifest sources of leverage (e.g. threat of trade sanctions). While several of the mosquito DARTs push up against the limits, none has yet – yet – pierced the envelope of acceptability to the point of a ban.

The urgency of the problem, and its uncontested status as a moral and global 'bad', combine with can-do narratives of technological success and non-state action in the face of establishment incompetence. Together, it manufactures a legitimacy for DART programs aimed at disease; that legitimacy may establish precedent for other DART applications. It is not necessarily a stable situation, nor one beyond critique. This is a suite of projects that deserves ongoing close inspection.

5.4.3 Epistemic norms

The norms of an epistemic culture can exert considerable effect on their activities and discourse, both internally and directed out onto the world. In the cases of DART research we have examined, we can see this occurring in at least two ways. In possums, the emergence of an epistemic community around invasive species management came in lock-step with the emergence of a disciplinary norm about what could and could not be done with DARTs, and even if their research could be pursued. In mosquito DART research, it was the expression of audacious goals by unorthodox but powerful actors that created an environment in which DART research not only was credible, but is a necessary part of the package for achieving it. The norm at play here is one of credibility.

In their defence of the possum DART, (Cowan et al. 2008) were keen to separate 'research questions' of a technical nature – which would involve the continuation of development of the technology (or its components) so they may be tested as disinterested scientific phenomena – from socio-political questions. In doing so, they emphasised collaboration across the Tasman Sea between Australian and New

Zealand research communities (also see Appendix 1)[18]. This manoeuvre resonated strongly with the Australia DART programs. It was a permissive, but cautious, pro-development stance. It ensured a substantial bloc of stakeholders could advance their careers, delivering the countable metrics of papers and patents and PhDs that a neoliberalised approach to R&D funding requires, but still stopped short of potentially disabling questions over the consequences of success, complete or partial. The signal was clear: we are like you. Since the early 1990s there was a steady trend of collegiate and increasingly formalised interactions with the invasive species science community across the Tasman Sea, including joint publications and formal inclusion in research organisations. A review of the dynamics and legislation pertaining to international issues in GM biocontrol that is frequently cited amongst this research community (Henderson and Murphy 2007) is a co-authored work between an Australian pest control researcher and a senior member of the New Zealand Department of Conservation, both of whom are part of the Australian-based Invasive Animals Co-operative Research Centre.

This is the evolution of an epistemic community (Haas 1989), but one that, rather than capturing the policy and political agenda of their respective jurisdictions, has been captured by it. Arguably, the price of admission has been to drop DART research. While years of investment failed to overcome many of the technical hurdles encountered in the Australian DART programs, promising leads emerging at the end of the funding bloc were not incorporated into the new funding bid for the Invasive Animals CRC. In New Zealand, the relevant government agencies have simply withdrawn funding for possum biocontrol, and key staff in the DART program moved away or joined other projects. There is a strong indication, therefore, that a norm has developed that plays a part in constituting the identity of the epistemic group, but also works to discipline its members, who will self-censor themselves (at least in their funding bids) and exclude non-conformers. This could be considered cynically as a realpolitik manoeuvre designed to secure funding and career progression.

Equally, however, it could very well be the outcome of an import piece of learning in DART research. Technology developers and the wildlife management community may have recognised that there are social limits that preclude the development of such DARTs, and/or have indeed have concluded that DART research is not a wise idea itself. Coming out and declaring such a conclusion carries significant risk in a neoliberal funding environment in which success breeds success (Martin 2000) and culture(s) that historically have found cause for rejoice at the downfall of its own rising stars (Phillips 1950; Feather 1989). If this is true, it is a disappointing loss of a learning opportunity and useful precedent, (similar reasons to the failings in quiet bilateral resolutions to conflicts over DARTs; section 5.4.5 Political risk aversion). Certainly, publications produced as summary and synthetic of these work programs carry an introspective and reflexive note (Hardy and Braid 2007; Strive et al. 2007; Van Leeuwen and Kerr 2007; Weihong 2009; Saunders et al. 2010). Again, Hederson and Murphy's (2007) highly regarded article on DARTs for biocontrol looks like an instrument signalling a quietly negotiated consensus.

In mosquitoes, DART-based solutions have entered the fray in a kind of dialogue with a larger vision of malaria eradication. There has been an iterative validation of

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[18] Cowan and colleagues (2008) also pointed to provisions of the Cartagena Protocol and New Zealand's *Hazardous Substances and New Organisms (HSNO) Act 1996* that would adequately govern at least some of the risks involved.

the imaginaries of molecular science on the one hand, and the imaginations of rich benefactors on the other. Together, they have created an epistemic environment where it is permissible to speak about the audacious – and previously *in*credible, and hence taboo – goals of eradication and mosquito population replacement without risking the loss of one's professional credibility. (Indeed, it takes one step further, and such imaginaries are vested with a moral rectitude, discussed above). Although we saw the circumstances by which that occurred in the discussion of broader political legitimacy, it is worth looking at its antecedents in more detail.

Taking up the director generalship of the World Health Organisation in 1998, Gro Harlem Brundtland reinvigorated interest in malaria control by declaring a new "Roll Back Malaria" campaign (Nabarro and Tayler 1998; a perfect example of the shift to hybrid governance models on the international stage, with involvement from governments, NGOs and all sorts of organisations in between). Six years later, the influential British Medical Journal published a none-too-flattering editorial (Yamey 2004), declaring it a failing campaign in which promises of funding had not materialised (e.g. Narasimhan and Attaran 2003) and relatively simple options were poorly implemented (particularly, insecticide-treated bednets, insecticides and artemisinin-based medication). It all seemed like history repeating itself, with the de-motivating memories of the 1950s and 1960s failure of the Global Programme for Malaria Eradication (Tanner and Savigny 2008; Greenwood 2009) still clear in people's minds. Expectations of success seem to have been, politely, rather modest. The notion of "eradication" of malaria was seen as naive or even taboo (Greenwood 2009).

The epistemic community of infectious disease control was forced to review its understandings of the situation, however, because of the two events disclosed previously. Firstly, it became clear that progress was indeed possible. Credible authors documented that in at least a limited number of cases, campaigns focusing on insecticide-treated bednets and medical interventions targeted at the most vulnerable sectors of the human population (mothers and infants) managed to reduce malaria incidence by up to half (UNICEF and Roll Back Malaria Partnership 2007). Here was hard data that worked, firstly, against the evidence of previous failures, and secondly, gave empirically grounded plausibility to the ethical motivation of reducing disease and suffering.

Then came both the money and the will, stitched together in one technoscience-friendly package: the Gates Foundation. Here was the wife of one of the world's most scientifically literate and pragmatically influential people telling this epistemic community that eradication was the new objective. The influential journal, *Science*, reported the event with an article entitled, "Did they really say… eradication?" (Roberts and Enserink 2007). The fact that the position was backed by a man who had a central historical role in taking scientific curios and making them into tangible, ubiquitous and indispensible machines – and the sheer weight of wealth – enabled the statement to endure defeating critique that might end a lesser, scientific professional's career. Amid pubic spin that attempted to pull back the audacious goal to the more achievable "elimination" (see Box 4.2.2 for distinctions), the audacious goal was quickly reaffirmed by none less than the WHO and the Roll Back Malaria campaign (Greenwood 2009).

The enrolment of these major players into a global scale project – carrying with it a large amount of moral legitimacy – has now created an environment in which funding and opportunity is *provided* by pursuing previously outlandish goals of population replacement and GM insects. Mosquito DARTs are now ‘hot’ research projects, with high public visibility (e.g. media and *Nature* attention to the technologies). This is interesting in itself, historically and sociologically. It also warrants exploration, to investigate how the grandness of vision here may work to validate (or overshadow) technoscientific trajectories elsewhere.

5.4.4 Brinkmanship

There is an institutional structure of research and development of DARTs that leads quickly to a point of brinkmanship, at least within neoliberalised Western cultures. A clever DART idea, playing to the interests of enough of a critical mass of stakeholders within the research, funding and governing networks, may be advanced under the mantle or ‘research’, with the legitimating cover that approval for release has not yet been granted.

In late 2003, an international conference on wildlife management held in Christchurch, New Zealand, held a special session on GM biocontrol, at which this research program was presented, along with work on Australian and Spanish efforts. In concluding remarks, the consensus opinion in the session indicated a ‘proceed with caution’ attitude, and an undertaking to keep all parties informed. But there is also an international dynamic, of which only part is readily visible. In their defence of the DART, Cowan et al. (2008) were keen to separate ‘research questions’ of a technical nature – which would involve the continuation of development of the technology (or its components) so they may be tested as disinterested scientific phenomena – from socio-political questions. In doing so, they emphasised collaboration across the Tasman Sea between Australian and New Zealand research communities (also see Appendix 1)[19]. This rhetorical and epistemological manoeuvre, in which value-free investigations into a possible technical solution legitimate the development of the biocontrol agent – ultimately to the point at which it could be put into use – has also been used in Australia’s DART programs. It is a permissive, but cautious, pro-development stance. It ensures a substantial bloc of stakeholders – the scientists, students, administrators and the managers of the programs under which they labour – can advance their careers and explore questions and possibilities of interest, delivering the countable metrics of papers and patents and PhDs that a neoliberalised approach to R&D funding requires, but still stops short of wrestling with the unpleasant, possibly disabling questions of responsibility, wisdom and the consequences of success, complete or partial. Of course, as was often remarked in these circles, without such research into the development of the DART, there would be no solid data upon which to base an evaluation of risks and benefits, which is undeniably true. This is a dynamic that will be instantly recognisable to all STS scholars. It is a structure of interest that leads to brinkmanship.

Since the early 1990s there was a steady trend of collegiate and increasingly formalised interactions with the invasive species science community across the Tasman Sea, including joint publications and formal inclusion in research organisations. Even though the New Zealand DART program posed risks to

[19] Cowan and colleagues (2008) also pointed to provisions of the Cartagena Protocol and New Zealand’s *Hazardous Substances and New Organisms (HSNO) Act 1996* that would adequately govern at least some of the risks involved.

Australia, elements of the Australia DART research community may well have understood that to argue against New Zealand's possum biocontrol would quickly lead to a de-legitimation of their own research program.

Many questions about DARTs in development cannot be definitively answered without an organism with which to experiment, especially in the quantitative sense demanded by risk-assessment frameworks. Logically, this is hard to refute. Strategically, it constructs an umbrella framework under which a variety of research and development agendas can be grouped, share information, continue dialogue, and indeed, procure funding for research and people's careers. But it must also be noted that this manoeuvre works to hide the divisions amongst the research community, to defer the resolution of controversy and permit the continuation of (potentially risky) product development up to the point of usability. In funding schemes that measure productivity by counting deliverable products, and political environments that are national in focus – sometimes the subject of volatile politics liable to spurts of decisive, symbolic but ultimately unwise action – this rhetorical move is inherently dangerous.

5.4.5 Political instrumentality: green neoliberalism

Some DARTs can be viewed as a strange political boundary object, attempting to bridge long-standing divisions between the pro-development, anthropocentric and capital-accruing right, and the pro-environment, socially-progressive left. In this sense, it is another example of science and technology creating politics (Jasanoff 2005). It also marks, or is perhaps the hallmark of, the entry of neoliberalism into society's relationship with nature, (Castree 2008a; b), although I am unaware of its documentation as such. This deserves exploration.

Consider that in New Zealand's possums lay an unusual coalition. The pest animal was closely associated with disease, bovine tuberculosis, threatening the ordered claim of domesticated production that had been carved out of a daunting wilderness and stitched into national identity within only the past few generations, and threatened the newly conceived competitiveness in a global marketplace in which nations are brands and products are "pure" and "clean" meat and transformative tourist experiences. Here too was a voracious threat to the wild nature that different sections of New Zealand society valued in their own, conflicting ways – on the one hand, the endemic and dying biodiversity of this far-flung island chain was being destroyed, and with it, the components of that wilderness that spoke of rugged independence and valued difference in the world (important to a nation of 4 million people), an ecological extraordinariness and biological wonder that made the objectives of the green movement so much more manifest. On a variety of timescales and from a diversity of perspectives, possums were (and remain) an evil spreading plague threatening the very essence of New Zealand-ness itself. The fact it was Australian probably didn't help[20]. Here in possums was a common enemy that conservationists, industrialists and technological enthusiasts alike might find a patch of common ground[21].

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[20] The relationship between Australia and New Zealand, although with very different historical antecedents, is roughly equivalent to that between Denmark or Sweden and Norway, although the Australian economy is stronger and continues to attract New Zealand emigration.

[21] In 1999, the neoconservative National Party lost government to a coalition of Labour and Green parties.

Whether a biotechnological solution could be agreed upon, in a nation that had deep and acrimonious debate over genetic modification (see, for example it's Royal Commission on genetic modification; Eichelbaum et al. 2001), was an unsettled question. The use of genetic modification was generally understood to make the strategy more difficult to sell to the public (e.g. as reflected in (Parliamentary Commissioner for the Environment 2000) and the NSSC listed "research into public and Government opinion" as one of two goals for the work, although as a much less developed statement than the technical one preceding it (Atkinson and Wright 1993). At this level, the selection of immunocontraception as the mechanism of a biotechnological strategy may have had something to do with the fact that animal welfare was long known to be an important factor in public acceptability in possum control (Sutherland and Orwin 1996; Parliamentary Commissioner for the Environment 2000; Wilkinson and Fitzgerald 2006) – contraception is far more palatable to the compassionate than is death by disease or starvation, considered as an alternative mode of DART action.

The fact that this research program was wound down by administrative fiat, most likely at the invisible hand of diplomatic pressure, robs us of the opportunity to see if such a DART would in practise be accepted by these two factions, and in so doing fulfil a unifying technopolitical goal it shares with the like of Golden Rice (Cyranoski 2005). It seems reasonable to assume that mosquito-based DARTs, and particularly other DARTs aimed at conservation goals (see Box 4.1) may work to or be devised to serve similar purposes. It is worth considering, too, that other nations and geocultural groupings may have their own longstanding schisms. As technological capacity builds rapidly in these countries (Brasil, China, India, etc), we should look to their internal motivations and the technologies they spawn, also.

5.4.6 The institutional cultures of DART research

DART programs are, of course, sites of large inflows of capital, people and effort. They are able to exist only because of the institutions that exist to support them. Each of these institutional settings, however, constitutes a particular environment or culture in which the research is conducted, and indeed its use imagined. While epistemic cultures are dealt with in 5.4.3, it is worth examining three very different institutional cultures arising just from the two case studies we have examined here. Each has a bearing on the development of DARTs.

The different status of possums in Australia and New Zealand saw very different research cultures develop across the Tasman Sea (Clout and Sarre 1997), cultures embodied in the institutions where the research took place. New Zealand was interested in killing possums, and research to this end was more locally relevant (New Zealand ecology) than Australia's predominance in 'basic biological' research. New Zealand hosted a program of applied science across its agricultural and conservation science departments. The development of the possum DART (and its alternatives) was carried out by government-agency employees reporting to governmental lines of authority and operational managers. For a long time, New Zealand possum research, including the development of the DART, was published mostly as government reports or in New Zealand-specific journals, poorly visible outside of a restricted network in New Zealand. This was a New Zealand problem, for New Zealanders to solve. Only towards the end of the program, as the profile of the work grew and Australian interest was manifest (see section 5.4.3), and scientific and financial links across the Tasman deepened and formalised (see Appendix 1), did the

New Zealand DART community emerge into the full spotlight of international science, media and politics. It did not fare so well.

While a small set of innovative approaches preoccupied a small group of scientists in nationally-interested organisations in the Antipodes, mosquito born disease attracts a very large number of researchers, diverse sources of funding, and a remarkable proliferation of technological ideas actively being pursued in a suite of organisations of international focus. The institutional setting could hardly be more different. Not co-incidentally, the DARTs developed here are enjoying a different trajectory. While this network of institutions beings its own dynamics that warrant exploration, the most striking difference here is the Bill and Melinda Gates Foundation.

Why should, as some saw it, the naïve wishes of a rich man's wife for a world without one of humanity's oldest foes prompt such an acquiescent response? Because Bill and Melinda Gates possess a heady combination of money and power, and they are using it. Box 5.4.1 details the Gates' Foundation's involvement in DART research. Their entry into the fray with is perhaps one of the most visible signs of a new (techno-)social force, philanthrocapitalism (Bishop and Green 2010), or venture philanthropy (Frumkin 2003). Another institutional bloom under the rising sun of governance (and neoliberalism), philanthrocapitalism takes practises, organisational and production models, a return-on-investment financial mindset, technology, personnel and capital from contemporary business and applies them to goals that have historically been most often assigned to organisations of strongly governmental origin.

Box 5.4.1 – DART strategies and the Bill & Melinda Gates Foundation's Grand Challenges in Global Health

Adapted from http://www.grandchallenges.org/

GOAL 3: Control Insect Vectors

Insects spread many serious diseases… [U]sing insecticides to kill disease-transmitting insects … has met with mixed success. A number of promising approaches … include genetic strategies and heritable biological control strategies to reduce the numbers of insect vectors or to inhibit their ability to transmit a pathogen...

CHALLENGE 7: Develop a Biological Strategy to Deplete or Incapacitate a Disease-transmitting Insect Population

Proof-of-concept laboratory experiments have demonstrated that genetic strategies and heritable biological control strategies can reduce substantially the capacity of insect vectors to transmit disease agents. Furthermore, similar strategies have succeeded in reducing or eliminating certain agricultural pests. While we can enumerate the technological requirements for the control of disease-transmitting insects, we have not solved the full range of problems that would allow us to either replace an insect vector population in the field with one incapable of transmitting a pathogen, or to control insect vector population numbers by genetic approaches or by heritable biological control approaches. We also cannot accurately predict all of the ecological consequences.

Challenge: To develop a coherent strategy either for making vector populations incompetent to transmit disease agents or for substantially reducing the prevalence of the vector, by the introduction of genetic constructs or microbial agents. The strategy must ensure effectiveness in the field, safety, and social and environmental acceptability….

Potential Benefits: Permanent disruption of the disease transmission cycle, achieving prevention without need to treat the human population

Priority Areas

* Malaria
* Dengue and other tropical arboviral diseases

Projects

- Establishing Dengue Virus Refractoriness in Natural Populations of *Aedes aegypti* Mosquitoes
- Genetic Strategies for Control of Dengue Virus Transmission
- Homing Endonuclease Genes: New Tools for Mosquito Population Engineering and Control
- Modifying Mosquito Population Age Structure to Eliminate Dengue Transmission

[*See also the following references: (Chen et al. 2007; Lavery et al. 2008; McMeniman et al. 2009; Mumford et al. 2009; Atkinson et al. 2010; Matsuoka et al. 2010)*]

The field of philanthrocapitalism is closely associated with the new fortunes and culture of high technology (Hero 2001; Fruchterman 2004; Birn 2005; Edwards 2009; Smith 2010). Google, for example, has a dedicated philanthropic arm, Google.org (Hafner 2006), and some organisations (e.g. Benetech[22]) specialise in taking technology that has failed to meet the particular rigours of orthodox market dynamics and apply them to charitable or social goals. This is an important feature for our focus on DARTs. Whereas in New Zealand, public sector science employees worked to satisfy nationally-bounded government policy objectives in developing a DART, and were ultimately left unfunded by a policy shift, here is a suite of high-powered, globally-oriented actors comfortable and familiar with the risks and rollercoaster rides of technology development, able to quickly move large flows of resources into selected targets, and ruled by much shorter chains of decision-making. Moreover, there is arguably a predisposition amongst these actors to search for a "technological solution"[23]. This is talked about in positive terms by the technologist-philanthropists themselves, but also forms the core of some well-placed criticism (e.g. Birn 2005).

Nevertheless, the most important feature for our concern here is not so much the details of the project but rather the simple and profound fact that the Gates' high-tech and high-powered entry to the field has created an institutional culture that legitimates radical imaginations for solutions, all the more critical at a time that technological prowess is reaching the stage in which they may be brought into being.

Private for-profit interests are significant change in the institutions moving in disease control, too. Oxitec is a spin-off company from Oxford University, (United Kingdom) that has been created to develop and sell genetically modified insects for their population control (see Box 4.2.3). Led by an energetic CEO, Luke Alphey, their business is built around a technique called the Release of Insects carrying a Dominant Lethal, or RIDL (Thomas et al. 2000)[24]. Their company has a dedicated regulatory affairs officer, Camilla Beech, and has conducted the world's first release of a transgenic insect, an experimental release of the pink cotton bollworm in the United States. Although the insect was engineered only to express a fluorescent marker – that is, it was scientifically an experiment in monitoring the dispersal of a GM insect – it was also an experiment in pushing the regulatory envelope. It was this release that lead to the publication of the world's first official risk assessment for the use of GM insects in the field (Fox 2004; USDA 2008).

In the scientific literature on transgenic insects, Alphey and Oxitec are prolific. In the popular press, Oxitec's approach is highly visible, partly because it is so advanced in its product development, and partly because of their keenness to engage with the media. Oxitec and its staff are well-embedded in the vector control and public health community, too. For instance, Oxitec staff are part of the WHO[25]-funded MosqGuide project, an international collaboration to provide guidance and training in using GM (Mumford et al. 2009). Oxitec staff was again heavily involved in the running of a

[22] http://www.benetech.org/

[23] It is worth noting, however, that in the bulk of these discussions, "technology" often denotes electronic and computing innovations, but with important exceptions (e.g. the drugs-for-the-poor model of Oneworld Health; McKerrow 2005).

[24] Contemporaneously and independently, Jörg Heinrich and Maxwell Scott, based in New Zealand, published results of a very similar approach (Heinrich and Scott 2000).

[25] In fact, the WHO's Special Programme in Research and Training in Tropical Diseases (TDR), that is in itself a collaboration between UNICEF, the UNDP, the World Bank and the WHO.

UNDP-sponsored Workshop on the Risk Assessment of Transgenic Insects in November 2008, part of Malaysia's capacity building program in biosafety under national and international law (Beech et al. 2009a). At least one of the three scenarios considered was based on a release of proprietary RIDL technology.

Perhaps not coincidentally, this case – a RIDL-based release of sterile GM *Aedes aegypti* – is currently being brought into reality in Malaysia (Department of Biosafety Malaysia 2010; National Biosafety Board 2010). This application is a joint effort with the Malaysian Institute for Medical Research (IMR), spearheaded by S.S. Vasan, also an Oxford graduate, who has been involved in local work with Oxitec's technology.[26]

We can see two things in this. Firstly, spin-out companies are able to deliver technological devices that capitalise on originally publically-funded university research in a particularly dedicated and single-minded fashion. After all, there are similar technological strategies published in the literature from university-based and supra-national actors. Why has Oxtiec's approach been so materially fruitful? The ethics of making money from helping the global poor also begs special examination. However, the presence of an internationally mobile small company, producing DARTs and DART-like devices, does offer a particular instance to study the emergence of a regulatory network, as discussed in section 5.3. Oxitec has taken a very proactive role in the processes creating that regulation, both formally and – one can speculate – informally and without public record. This deserves exploration.

A second feature embodied in the Malaysian trial is the involvement of local actors. Involvement and support of local actors is widely acknowledge in public health literature as essential for programmatic success (Feachem et al. 2002; Williams and Jones 2004; Knols et al. 2007; Doyle and Patel 2008; Stratton et al. 2008; Kilama 2009; Klassen 2009; Mumford et al. 2009). Here, however, is a trial in which foreign-owned technology has been adapted to local conditions in a collaborative effort between a "rich Western" company and a "developing nation" public health science team. Malaysians are clearly taking ownership of this program – but exactly how far this claim can be pushed needs research. Notwithstanding, it does highlight the fact that the historical "donor-recipient" institutional setting of programs and project targeting development have begun to enter a very different phase, one in which power of social and techno-scientific natures may be more evenly distributed, or perhaps almost wholly endogenous. Discussions in a special session of a nano- and emerging technologies conference[27] in Trento, Italy this September suggests that this endogenous dynamic of technological development in the developing world warrants further dedicated investigation.

There are heritage and legacy issues at play here in mosquito DARTs' institutional environment. Public and supranational agencies like the Food and Agriculture Organisation and the International Atomic Energy Agency (see Box 4.2.3) and particular university departments around the world have been researching and

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[26] Vasan was also the guest editor of the special issue of the *Asia Pacific Journal of Molecular Biology and Biotechnology* (Volume 17(3)) that stemmed from the November 2008 UNDP-sponsored workshop.
[27] Society for the Study of Nanoscience and Emerging Technologies 2010. See http://www.philosophie.tu-darmstadt.de/nanobuero/snet2010/welcome.de.jsp. This session, *Emerging Technologies for and against Emerging Economies*, was organised by Arianna Ferrari and Paulo Roberto Martins.

executing vector control strategies with non-transgenic means for several decades. Molecular biologists, with their new tools, institutions and knowledges are new entrants to the mosquito control community. Some have clear vested financial interests in the form of the usual profit motive (as befits a business), whilst others have financial interests based on return on investment (as in philanthrocapitalism) and indeed a substantial vested interest based on the realities of career advancement in today's technoscientific and public health bureaucratic regimes.

5.4.7 Accountability

There is an expectation that governments should be held to public account for their actions. Although this accountability is a task of constant vigilance in society, the issue is well covered in other areas, and should be directly applicable here. However, the international implications of DARTs suggest that accountability to citizenries that are not one's own will be an important topic here. This is addressed in the section on liability regimes in 5.3.7. Two exceptional classes of actors in DART development raise important, and perhaps novel, questions about accountability.

Philanthrocapitalism, however capable and refreshing it may be to the world's needy, is not without its critics. Concerns over accountability form a major tranche of these critiques, as does accusations over lack of local knowledge, general expertise, the selection of targets for funding and a focus on material provisions, the long term sustainability of interventions, potential ulterior motives, and an extension of a market-based approach that may not be appropriate (Birn 2005; Edwards 2009; McCoy et al. 2009; The Lancet 2009; Smith 2010). These criticisms are important. Other institutions operating in the philanthropic sector have had to grapple with these and evolve a system of governance. But what of these powerful new entrants?

The techno-savvy and the Gates Foundation[28] controls an annual health budget equal to or larger than the World Health Organisation's (Birn 2005), around USD $3 billion per annum (The Lancet 2009). There is no easily accessible listing of the total amount of money granted by (a common critique of philanthrocapitalism; (McCoy et al. 2009), nor number of projects supported by the Foundation for the development of mosquito DARTs. Not all project supported by them (see Box 5.4.1) are listed on their websites, either: a project that has genetically engineered mosquitoes able to deliver vaccines via their bites is published in the scientific literature (Matsuoka et al. 2010) and was widely reported in the press (e.g. Johnston 2008), but is not obviously announced on their website, if at all.

The actions of private enterprise require scrutiny too, although the dynamics here may contrast with the business-as-usual modes of operation by large companies like pharmaceutical giants. Two Oxitec staff (including Beech, in the role of joint project manager) are included in the eleven participants in the MosqGuide project. This WHO-funded project is "intended to support disease endemic countries (DECs) and other stakeholders in considering the safety and legal/regulatory aspects, as well as ethical, cultural and social issues" in deploying GM mosquitoes for disease control, especially dengue and malaria. This includes the provision of training material for the WHO's work in biosafety and tropical diseases (Mumford et al. 2009).[29] Oxitec staff

[28] The even have their own watchdog website, charmingly named "Gates Keepers: civil society voices on the Bill and Melinda Gates Foundation". http://gateskeepers.civiblog.org/

[29] Mosquide is also envisioned as providing guidance that will dovetail with that developed by a Gates Foundation and US Foundation for the National Institutes of Health initiative on caged tests of GM insects (Benedict et al. 2008; Mumford et al. 2009).

was again heavily involved in the running of a UNDP-sponsored Workshop on the Risk Assessment of Transgenic Insects in November 2008, part of Malaysia's capacity building program in biosafety under national and international law (Beech et al. 2009a). At least one of the three scenarios considered was based on a release of proprietary RIDL technology. This is very similar to the Malaysian release that has just been announced (Department of Biosafety Malaysia 2010; National Biosafety Board 2010).

This constellation of factors requires some interpretation. There is no evidence to suggest that any malicious or corrupt dealings here. One might suggest that, in fact, Oxitec and the Gates Foundation are simply being responsible and initiating discussions and promoting the establishment of regulatory frameworks that are required before the DART applications are pressed into service, as has been called for (e.g. Angulo and Gilna 2008b; Angulo and Gilna 2008a). There is certainly a void (see section 5.3). A small set of names recur prominently amongst papers and documents relating to these developments. There is no indication that there is conspiratorial agreement, but it nevertheless bears witness to a small community of expertise and authority on these matters, united by the highly unobjectionable motivation to end human suffering at the mercy of mosquito-borne disease. This community is comprised of practitioners, managers, and technology developers, actors who very often are also the ones sitting at the table constructing the risk and regulatory frameworks that will govern these DARTs. Almost by definition, the compositions of these groups are heavily weighted towards experts from the global North (but not exclusively, e.g. MosqGuide).

Prima facie, there seems to be a serious imbalance in the range of perspectives that are being brought into manufacture the regime of governance of DARTS. This is a vitally import area that needs dedicated research.

5.4.8 Language and legitimacy

The rhetoric of pest and disease control is very often saturated with metaphors of war (Russell 1996; Larson 2005). (Indeed, it is very hard to write about these issues without resorting to such terms oneself). The military theme is not limited only to metaphors – institutions, systems of authority and accountability, planning and strategy, and the organisation and deployment of personnel and materiel are all liberally peppered with ideas and language borrowed from military operations.

"The fundamental biological principles of poisoning Japanese, insects, rats, bacteria and cancer are essentially the same." William Porter, chief of the Chemical Warfare Service, 1944 in (Russell 1996).

This martial entanglement is partly borne of necessity. Vector borne disease can and has inflicted greatly more mortality on armies than their human enemies. Experience in and tools from theatres of war quickly moved to civilian life, with military aircraft adapted from chemical warfare units conducting aerial sprays across cities and swamplands in last century's anti-mosquito campaigns (e.g. Russell 1996; Patterson 2004).

Militaristic metaphors and thinking now work to legitimate the recruitment of large quantities of resources, (material, fiscal and human) to be applied to defeating the 'enemy'. Reflexion about the framing of the issue becomes at best an irrelevance, or at worst an act of treachery. Such constraints are a trade-off, and the social contract shifts to acceptance of the poorer individual conditions under the promise of the payoff of victory and a restoration of previous freedoms. This deferment of basic privileges extends to the right – as now observed in some democracies around the world, but certainly not all nations – to consent before a risk exposure (Beck 1992). This "for the greater good" mentality was clearly on display, for example, in a recent televised debate between prominent Malaysians over the prospect of experimental releases of RIDL mosquitoes (Al Jazeera 2010).

Disease control policies often demand action by citizens, and involve strong measures against citizens that do not play their part. In Singapore, for example, not removing mosquito habitat can result in a substantial fine, and surveillance occurs formally by government staff, and more quietly by community informants. In other circumstances (e.g. Australia), species declared as a registered pest must legally be destroyed by landholders, and there are sanctions (legal and social) against those who do not. DART technologies can be very different. By their ability to spread and act without assistance, or at least minimal subsequent interventions, their use may not require such powerful exertions of control across other (human) elements in society. For example, there may be no *need* to prosecute householders who leave pools of water in pot plants and junk in their yards – society will intervene at a different locus, on different and non-human subjects to achieve a reduction in mosquito numbers. This is a technocratic solution to the democratic dilemma.

Ideas of security may be a useful trope to explore for DARTs – ongoing surveillance, ever-present threat within 'tamed' zones, the notion of (terrorist cells) and networks, of the role of 'softer' forms of power, and of continual exercise of power that curtails individual rights in the name of security and conservation of an existing order.

5.4.9 Communication

There are several processes at work that cause DART programs to develop without full visibility and scrutiny of the research and wider communities.

The tendency of research programs (like New Zealand's possum DARTs) that are highly nationalised to publish within national scientific outlets is discussed elsewhere in this report (e.g. section 5.4.6). The effect of this was the creation of a small, nationalised community of cognoscenti, at least from an international perspective. New Zealand is a well-developed nation with good communications infrastructure, and publishes in the widely understood language of English. The creation of a national community about a DART becomes more probable if the outlet of publication is not easily accessible through literature databases and internet distribution, and if the language is one in which few – at least in the Western world – have mastered, such as Russian or Chinese. The latter is particularly dynamic in its scientific endeavours, but one can surmise that only a fraction of this work is visible to Western scholars. Given the inherently international relevance of DARTs, this is a concern.

In the scientific literature on transgenic insects, Oxitec and its founder, Luke Alphey, are prolific. Oxitec's approach is highly visible in the popular press too, partly because it is so advanced in its product development, and partly because of their keenness to engage with the media (sensationalism notwithstanding). This strategy works to amplify their particular take on events and issues. This may not be appropriate.

Although it is dealt with in only the most cursory fashion here, the stance taken by popular media in all its many forms and locations is crucially important to the politics of DARTs and their use. The Al Jazeera broadcast on the Malaysian mosquito trial, airing a debate and perspectives of Malaysians themselves, is particularly noteworthy (Al Jazeera 2010). Historically, it would be interesting to chart the impact of the critical Australian television broadcast (Newby 2003) on immunocontraception in both Australian and New Zealand research policy.

The editorial tone of major scientific organs should not escape scrutiny, either. The influential journal *Nature*, and its subsidiary, *Nature Biotechnology*, appear to take a rather bullish line on mosquito DARTs generally, with cover-stories like “Green light for mosquito control” (Atkinson 2005, an opinion-piece analysing the significance of a regular scientific paper, Catteruccia et al. 2005). Just this year, it published a remarkably one-sided news piece “A world without mosquitoes” that advanced the case for the inconsequentiality of the removal of mosquitoes – of all species – from the general environment (Fang 2010). This is a concerning trend that deserves analysis and exposition.

5.5 Concepts of safety and risk

Issue of safety and risk circulate prominently in contemporary discourses on new technologies, and DARTs are no exception.

5.5.1 Safe by design

In Australia and New Zealand’s vectored immunocontraception, the specificity of the vector was envisaged as an important element of control. Indeed, it was perhaps the single most important legitimating factor that permitted its imagination. In Australia, a rabbit virus vector would cause infertility only in rabbits, a fox virus for foxes, and a mouse virus for mice, all species quite different from the bulk of native and valued species in that country (apart from the fox, which is closely related to domestic and native wild dogs) and thus securely isolated epidemiologically from everything else. New Zealand’s threatened endemic fauna are comprised almost uniquely of varieties of bird, and the placental mammals important to contemporary New Zealand culture are biologically distinct from the marsupial invader: possums are an evolutionary oddity on the archipelago. Separated by millions of years of evolution from any other host species (at least, in New Zealand), the *P. trichosuri* parasite, isolated from possums themselves, seemed to present a magic bullet, capable of infecting only the intended target. Like the best-intentions for other forms of biological control, the specificity of the host-disease relationship was recruited to the task of governing the DART right from its imagination.

In instructive contrast, the CRC for Conservation and Management of Marsupials (1995-2004) – a separate Australian research program in which New Zealand played a minor part – also investigated biotechnological means to control problematic marsupial populations including immunocontraception and hormonal interference. However, since the Australian cultural frame was overwhelmingly dominant, and *conservation* of native marsupials formed one of the constitutive goals of the research organisation, the delivery mechanisms considered were explicitly not auto-disseminating, focusing instead on an oral (i.e. bait) delivery (Rodger year unknown). The rationale to purse a bait-delivered contraceptive rather than a DART was a legitimating feature of the research, offering tight geographic and temporal control over the use of something that could cause significant reductions in native marsupial diversity. The problematic issue of governing DARTs was side-stepped at the beginning of the technology’s imagination (see also 5.3.1).

Safety by design is an overt attempt to draw lines of discipline into the essence of the DART object itself. This issue will be fundamental to the emergence of governance regimes for DARTs, and, as described in the section on epistemic norms (5.4.3) and in the introductory material on mechanical darts and nano-technology (3.1), operates in a way that powerfully influences the legitimacy of imagination[30]. While this is interesting in a sociological vein (e.g. see Box 2.1), it has practical implications for governance. For instance, WHO documents on ethical practise in the use and development of genetically modified insects has suggested engineering the biological equivalent of a 'kill switch' to be activated in the case of a trial going wrong (Macer 2003). Are engineered fail-safes reliable, and is it appropriate that more modifications should be part of the architecture of safety that legitimates trials? The stability of these design features, in an object that is capable of evolution, places fundamental but as yet unclear limits on this strategy. It requires review.

5.5.2 Have we learnt?

There is a sense of repetition in many technological risk issues– questionable or objectionable patterns of behaviour, rhetoric, distribution (of risk, power, etc) and consequences are repeated in another space and time. 'The usual suspects' (industrialists, government agencies looking for economic stimulus, etc) become technological proponents and are in turn met with resistance and protest by the 'usual suspects' of opposition (e.g. NGOs, globalised green groups and 'risk-based' scholars). Many of the participants in new controversies enter or are recruited from previous controversies, predisposing the dynamics of the new technological 'debate' to the turns and twists of recent history. The widespread anticipation of nanotechnology by both technological enthusiasts, (e.g. pro-development government actors), and risk-issue sensitive groups is perhaps the best example of this (Einsiedel and Goldenberg 2004; Mehta 2004; Kearnes et al. 2006).

The broadest and coarsest summary of these technological controversies is thus: proponent/s of a technological innovation (invented using arcane science not widely or long understood) cite realisable and significant benefits to society (and investors) in the technology, and note minimal or manageable probabilities of negative outcomes. Critics and opponents cite a range of negative consequences and impacts on (sub)populations that are tacitly and/or strategically underemphasised, under-investigated and understood, and often insufficiently weighted in contemporary decision-making frameworks (e.g. low probability vs. high magnitude events like nuclear accidents). One side sees roses, the other the thorns. It is difficult to try to delineate how much of these visions are genuine products of contesting worldviews, and how much are strategic figurations aimed at aligning an undecided or susceptible public, but there is surely a measure of both.

It can be predicted, therefore, that much of the critique levelled at DART will invoke tropes of recent controversies, especially like GM crops. Specifically, biosafety tropes include: wildly uncontained genetic elements propagating unpredictably through the environment, in several species, with irreversible effects; wildly uncontained organisms propagating unpredictably through the environment, with unknown and irreversible impacts on ecosystem composition and function.

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[30] See also new work on nanotechnology, safety by design and the evolution of proactive technological responsibility (Kelty 2009; McCarthy and Kelty 2010).

An alternative view of many of these attempts is much more positive: they are an example of how much we (as a global community) have learned from past mistakes (particularly in biocontrol and translocation), how cautious we have become, and we are being inventive in the face of dispersed (i.e. non-point source or diffuse), recurrent challenges that have, in times past, been met with rash, indiscriminately destructive responses (e.g. indiscriminate destruction of whole ecosystems like marshlands drainage, vilification of nature, etc.)[30]. Arguably, the DARTs we have considered here are the vanguard of a new technological negotiation with nature, mindful of necessary limits and caution, but also responsive of the enduring need to act against threat. As a line of evidence in this direction, it is worth reiterating that both research teams in Australia whose DARTs escape transgenics regulation (*Wolbachia*-based dengue control and daughterless carp) have declared that they want to go through a thorough process of risk assessment and community engagements (Hirsch 2005; O'Neill 2009; Fulton and Grewe 2010).

5.5.3 Political risk-aversion

Funding for the New Zealand possum DART has now ceased[31]. The research program that hosted the *P. trichosuri* work also included research on other, non-disseminating platforms for delivering immunocontraceptive material (including bacterial extracts (Walcher et al. 2008) and GM vegetables (Polkinghorne et al. 2005, deliverable as baits). This program was first subject to a review that used criteria that did not reward disseminating forms of biocontrol; the nematode work was suspended as the researchers pursued work that satisfied the review criteria. The Landcare Research New Zealand's page on possum biocontrol lists only a bait-delivered strategy under 'How will biological control work?' and 'How safe will it be?'; in fact the latter section declares there will be no live GMOs in the bait (Landcare Research New Zealand year unknown). In the latest turn of events, the funding agency's new priorities preclude *any* possum biocontrol. Key staff has left for other institutions (some in another country), including those central to the genetic modification of the nematode. Barring the possibility of other sources of funding, possum DART work in New Zealand seems to have been aborted.

This policy shift is at odds with the initial strategy that confidently declared "clear research priorities for biological control" of possums (Anon. year unknown), whose ultimate goal was nothing less than a "'permanent' solution" (quotation marks in original; (Atkinson and Wright 1993). Certainly, domestic politics have played a role in this decision. In a detailed piece of work, Wilkinson and Fitzgerald (Wilkinson and Fitzgerald 2006) report that although fertility control of possums was highly acceptable – particularly in light of toxic and inhumane alternatives – the use of GMOs to deliver it would be acceptable to less than half of the New Zealand public. They conclude that, "[i]f researchers are to continue to explore [GM bio-] controls, the most publicly acceptable strategy would be to concentrate on controls that did not involve the field release of live [GM] organisms…" (Wilkinson and Fitzgerald 2006):38).

Weihong (2009) suggests that anticipated controversy and resistance to disseminating forms of possum biocontrol over non-target impacts means that "a disseminating delivery system is not likely to be available for possum management in New Zealand". She notes in particular concerns in Australia over the threat to native

[31] The following information is from personal communication with a researcher central to the *P. trichosuri* work.

wildlife (Newby 2003; Gilna et al. 2005; Henderson and Murphy 2007). Considering that Australia is a major trading partner for New Zealand – a trade that biosafety-based trade sanctions could, legitimately, shut down (see section 5.3) – as well as a nation of strategic, transport and diplomatic significance, there is good reason to suspect that either a direct (unpublicised) approach from the Australians, and/or internal assessments enlightened by national and organisational self-interest all conspired to tip the scales of risk and benefit in favour of abandoning the DART program.

It is easy to mark this as a pleasing and appropriate outcome, one that is necessarily precautious. Indeed, given the facts of the matter, it is hard to think otherwise. However, just as much as political calculus can work to promote technological adventures that a cooler head would deem unwise, there remains the possibility of the same process of Machiavellian arithmetic shutting down difficult, contentious projects that may in fact be worthy of support. DARTs directed at alleviating suffering and extinction may be two such instances. Our scholarship, then, must play close attention to even-handedness.

5.5.4 Participation and its lack

DARTs, particularly in applications targeted at the most voiceless in global society (and here we may also pause to consider non-human living things) raise deep challenges to the ethical mandate to gain consent from affected communities. The only formal public research made available in the peer reviewed literature is a recent survey of Malians' attitudes towards the use of mosquito DARTs to combat malaria (Marshall et al. 2010). I can find no reference anywhere to public consultations or deliberations on the matter. For the proposed Malaysian experimental release of RIDL mosquitoes, advertisements were placed in local papers and an announcement of the application made online with a month's provision for public comment, although there is no evidence of more intense and localised forms of community consultation or procurement of community consent and, at time of writing, no on-line presentation of how the public comments received were taken into account in the decision-making process. Despite the prevalence of at least the on-paper acknowledgement of the need to gain some form of grounded community consent, action on-ground seems extremely sparse.

Reactions to the *Nature* pieces demonstrate that, while there is indeed scientific and bureaucratic excitement and momentum behind the application of this technology, it is not a uniform and unremittently techno-enthusiast movement[32]. In correspondence on it's "Green Light for Mosquito Control" coverpiece (Atkinson 2005), a group of senior authors from universities[33] and the joint FAO/IAEA Entomology Unit in Vienna concisely and convincingly set out a range of limitations of technical and ELSA dimensions on the unproblematic roll-out of transgenic mosquitoes (Knols et al. 2006). They state that the transgenic mosquito technology must be conceived of and reviewed broadly and "be integrated into a broader social context – a notion that larger development agencies like the World Bank … have recognized for many years, but which still appears to have eluded some scientists and funding bodies." They go on to articulate the greatest challenge in creating adequate systems of

[32] For reactions from a wider audience, see for example the comments section to Fang (2010), online at http://www.nature.com/news/2010/100721/full/466432a.html.

[33] The listed university is the University of Nairobi, but at least one other author has also been based at Wageningen University in the Netherlands.

governance for DARTs of any kind, that testing the technology to determine and refine its properties constitutes, in fact, a real release. For DARTs intended for the most underprivileged of the world's communities, the relevant release sites are located in nations whose communities are least empowered to participate in meaningful dialogue over the risks to which they may be exposed. Knols et al (2007) declare the "search for potential field sites to release transgenic mosquitoes ... [is characterised] by hastily established and cosmetic partnerships with scientists and institutions *in situ*."

In 2008, with funding from the Gates Foundation and the Foundation for the National Institutes of Health (see note 25, above), a consortium of researchers published clear, reasonable and well thought-through guidelines for the ethical conditions for the conduct of caged, semi-field trials of mosquito DARTs (Benedict et al. 2008). They are consistent with the widely cited 2006 paper by Macer on ethics and community engagement on GM vector release (Macer 2006), and another consortium of researchers' 2008 paper on site selection and ethical, social and cultural considerations in GM mosquito trials (Lavery et al. 2008). All include the need for community consent. They have not been publicly disputed. In other work, (e.g. Williams and Jones 2004; Knols et al. 2006; Knols et al. 2007; Stratton et al. 2008), researchers and practitioners repeatedly highlight the strategic and operational importance of community consent and support. These are not strategies of opposition by protest groups: several of the most prominent authors have written positively about the potential of DART techniques in the struggle against serious disease, especially in light of the limits of other strategies (Knols et al. 2007; Takken and Knols 2009; Knols and Schayk 2010). Again, such strategically-minded calls for consultation and consent are not visibly disputed in the peer reviewed literature, even amongst the most ardent technology proponents (e.g. Atkinson 2006; Beech et al. 2009b).

5.5.5 Ethics, risks and decision-making

DARTs have the potential to present us with difficult choices and decisions. Is it right to exterminate a species because they threaten us with disease? Is it right to apply an irretrievable technology? At what point do predictions of benefits overcome uncertainties about environmental costs, and how is the exercise of precaution balanced against the certain costs of inaction? Is there a horizon in time beyond which an inventor or 'releasor' of a DART is no longer responsible for unforeseen consequences? A development of these questions – and more – is of course beyond the scope of this paper, although scholars have entered the field already.

Again, there is a something of a sectoral division. For example, the prospects of releasing[34] modified insects for control of human disease has attracted statements by at least one ethicist (Macer 2005; 2006) and a range of principles and guidelines by researchers and vector-control practitioners, with and without the co-authorship of ethicists (Touré and Manga 2005; Lavery et al. 2008; Beech et al. 2009b; Kilama 2009; Lavery et al. 2010). The WHO Special Programme for Research & Training in Tropical Diseases[35] have published a set of recommendations (Macer 2003), repeated again by key staff (Touré and Manga 2005) that generally summarises the main points of consensus. In brief, they are:

[34] See (Benedict et al. 2008) for statements on caged trials by a large working group funded by the Gates Foundation and US Foundation for the National Institutes of Health.
[35] Joint funded by the WHO, UNDP and the World Bank

- The best scientific knowledge should be gained and used to minimize risks and uncertainties before trials, including data on the vector, the modification and the release site.
- Transparency, including open access to data and no excessive restrictions to protect intellectual property
- Information provision to the local communities
- Participation in decision-making, including community level consent

Issues of site selection and the difficulties in obtaining meaningful consent of local communities are emerging as one of the most important issues (Lavery et al. 2008; Lavery et al. 2010). How widely upheld these principles are in practise is another question that deserves independent investigation. It seems ironic that Oxitec, whose staff feature prominently (including lead authorship) on a paper describing progress towards best practise in genetic vector strategies (Beech et al. 2009b) should also be at the centre of field trials in Malaysia where it seems application to the authorities was made without prior approval – or even notification – of communities in the nominated areas (Al Jazeera 2010; Department of Biosafety Malaysia 2010). Despite the acknowledgement of the need for clear and universally respected ethical guidelines in their use and development, no such consensus has yet been reached (Macer 2003; Lavery et al. 2008; Beech et al. 2009b; Kilama 2009; Lavery et al. 2010).

On the other hand, a different set of authors have written about the ethical implications of DARTs for biodiversity conservation, particularly the prospects of non-lethal control measures offered by things like immunocontraception. In invasive species control, an ethical tension often surfaces between the welfare of the invasive animal and that of the broader ecological community. Within limits of uncertainties about the technique and questions about an animal's right to reproduce, immunocontraception generally has emerged as a favourable resolution (Oogjes 1997; Singer 1997; Eggleston et al. 2003; Morris and Weaver 2003).

There is interest in a specifically *ecological* branch of ethics, that would assist managers of ecological systems and conservation programs in making difficult decisions over implications of DARTs, but also species relocations and other radical interventions as brought about by the global environmental crisis (Minteer and Collins 2005a; Minteer and Collins 2005b). This has not yet translated into guidelines or norms about the ethics of DARTs derived by genetic modification. As of 2005, the Australian Gene Technology Regulator advised that it did not have the legal power to refuse a licence for deliberate environmental release of a GMO on the basis of harm to other jurisdictions (pers. comm.), but its subsidiary ethics committee included such concern in their draft of ethical principles for gene technology research (GTEC 2006). There is, however, an older body of literature that dealt specifically with the ethics of non-GM biocontrol, which is rooted in an ecocentric approach (Lockwood 1996). While the scientific and pest management communities maintain an interest, discourse seems to be more centred about issues of risk and benefit than a specifically ethics-based approach (e.g. Louda et al. 2003; Louda and Stiling 2004; Delfosse 2005).

All this, of course, must be interpreted against the vast body of thought on the ethics of the ecological crisis in which we find ourselves (a review of which is beyond the scope of this report). Nevertheless, a specific engagement with the thorny issues of

DARTs, including the radical propositions offered by contemporary biotechnological techniques, seems curiously underdeveloped. It is certainly not well integrated into discourses on DARTs in human disease control, although there is a small, Australian body of work that has pursued issues of immunocontraception, wildlife disease, and law that recognises continuity with human disease present in wildlife (McCallum and Hocking 2005; McCallum 2009).

Within the realm of decision-making and risk management, DARTs and their applications may form a particularly sharp disruption of the manner in which precaution is mobilised. Malaria control is the clearest example. Here, a disease causes massive suffering for some of the world's most vulnerable, and the best assessments of the situation – drawing on decades of successes and failures – demonstrate the absolute necessity of vector control, but also demonstrate that each approach to it has limits of effectiveness and carries its own risks (Stratton et al. 2008; Takken and Knols 2009). In many cases, resistance and disinvestment mean that effectiveness is becoming even more limited than it is now. An integrated strategy that uses existing tools, and necessarily including new tools is essential to make progress against human suffering (Hemingway et al. 2006; Takken and Knols 2009). Mosquito DARTs are some of those new tools. If we take an ethical stance that suggests human suffering should be reduced – as many do – there exists a powerful argument for deploying DARTs against these diseases and their vectors. But what does precaution look like in this application?

The Precautionary Principle, perhaps one of the most significant political achievements of recent decades, is often invoked to constrain the over-eager application of novel, powerful, but unfamiliar technological ventures. In this case, however, the ethical impetus may in fact work through the Principle to promote the use of a DART. To illustrate the point, consider the version of the Precautionary Principle advanced by UNESCO:

"When human activities may lead to morally unacceptable harm that is scientifically plausible but uncertain, actions shall be taken to avoid or diminish that harm."

Morally unacceptable harm refers to harm to humans or the environment that is

- threatening to human life or health, or
- serious and effectively irreversible, or
- inequitable to present or future generations, or
- imposed without adequate consideration of the human rights of those affected."

(UNESCO and COMEST 2005:14)

Diseases like malaria are serious, entrenched threats to human life and – as is increasingly being understood (see Appendix 2) – work to doom whole societies to underdevelopment, condemning their members and their children to global inequity. They clearly qualify as "morally unacceptable harm" as defined here (indeed, as they long have by many definitions). This raises uncomfortable questions. Does withholding the use of a technology that plausibly, but with irreducible scientific uncertainties, may lead to the diminishment of such moral harm, constitute the very kind of action that the Precautionary Principle works against? Further, would withholding the use of a DART, therefore increasing the reliance on other forms of vector control like chemical sprays and habitat destruction, exacerbate known environmental harms, also violating the objectives of the Principle? Do we really mean that the Precautionary Principle could work to advocate the use of radical, irretrievable technologies?

The treatment of uncertainty seems to lie at the heart of this paradox. Does the moral weight of certain human suffering trump the uncertain hazards of a technology whose first field test will, in fact, be its irrevocable release? What criteria or principles or procedures might be used in deliberating about the moral acceptability of uncertain harms against certain ones? These conundra resonate with signals emerging from other fields (e.g. food and crop biosafety). Many of today's jurisdictions systematically consider risks, but do not systematically weigh or assess forecast benefits (e.g. see recommendations of the SAFE FOODS project; Kuiper and Davies 2010; König et al. 2010). Like the negotiations over the Cartagena Protocol, balancing social disquiet and scientific uncertainties against multinationals' GM crops and hyperbolic promises may have been foremost in legislators' minds when creating their biosafety laws. Acting to minimise risk and relying on proponents to push benefits may have been a pragmatic choice. However, using DARTs against diseases of the poor and for urgent conservation is very unlike the scenarios in the rhetorical cover of profiteering agroindustrial giants. The pragmatic choice to avoid the systematic assessment of promised benefits and formal reconciliation with risks will need revision.

Other systems have already ventured into this arena, but are incomplete. The Norwegian Gene Technology Act (1993, amended in 2005) stipulates that the technology's contribution to sustainable development and the benefit of society be weighed into decision-making for deliberate environmental release. However, the Act also declares that releases will not be approved unless there is no risk of adverse effects to the environment. While both imperatives are laudable in themselves, DARTs clearly pose plausible risk – and may in fact be designed to *destroy* a part of the environment – but may be designed specifically to promote sustainability and social welfare. *Prima facie*, this creates an inherent contradiction in the Act that will need to be resolved. Other jurisdictions will have similar issues.

Can decisions about DARTs be made under existing risk management frameworks, or will they be found wanting? Could precaution, now the operational core of major pieces of important regulatory frameworks, be construed as immoral and uncompassionate, or unexpectedly technologically adventurous? If so, what is the future for precaution? What are the appropriate evidentiary thresholds for the likelihoods of harm and benefit, and how much uncertainty is tolerable when we trade them off against each other? Are these conditions the same in all cases[36]? Navigating this 'new' space in such a way not to destroy the hard-fought-and-won gains of the recent past, and yet create workable frameworks to inform decision-making, is a vitally important task that deserves immediate attention.

5.6 Governance revisited.

The reconfiguration of the practise of governing – particularly the governing of technological risk – to governance relies on recognising and authorising people and (non-state or hybrid[37]) institutions to control the actions of and create the spaces for their devices, living and non-living. The moves to participation in governance, while

[36] For example, Eurobarometer reports (European Commission 2005a; b) frequently show greater acceptance of GM technology for human health than agricultural production.
[37] "Hybrid" here referring to state and non-state, rather that semantic and material.

most often described as measure to increase democratic legitimacy and redress the epistemic failings of reductionist science, are also discriminatory: the invitation to participate in deliberating over a future is extended only to humans. Similarly, moves towards precaution are attempts to constrain the agency of things, typically before they ‘get out’, get out of control, or reveal themselves. Government seeks to work in partnership with other human agents in society to co-operate in exerting, in ever stronger, more reliable and more precautionary ways, power *over* non-human undesirably autonomous agents.

There are several layers of irony here. Many of these autonomous, dispersing technologies (DARTs) are being developed to be deployed against invasive species. Either by reductive, colonial worldviews that sought to extend a particular natural-cultural regime to ‘new’ lands or by accidental introductions of invasive creatures that hitchhike across the globe with international flows of goods and people (Rolls 1969; Griffiths and Robin 1997; Low 1999), problems with invasive species have their origins in the same problematic understanding of the world that has produced life under the shadow of technological mishap. Both DARTs and the move to governance are responses to problems of the same origin. In other instances, DARTs are being developed to combat disease vectors, particularly mosquitoes. Mosquitoes, like many of the insects and other small forms of life that we cannot shoot, fence or otherwise exclude from our settlements, represent a constant reminder that the modern conceptual device of splitting the world into the internal order of civilisation and the wild, external Other is fundamentally flawed. Indeed, as climate change starts to facilitate the spread of mosquitoes and disease, we are once again reminded of the failings of reductionist, linear models of the world in which we live and the pervasive dangers our technological apparatus has generated. DARTs are being engineered to combat these ‘flaws’. As such, this class of object that is so difficult to govern may in fact become a tool to establish a framework of governance at another scale.

6 Conclusion

Clearly, DARTs raise a number of issues that warrant further investigation. Their deployment marks a step-change in the way in which our modern culture – including the modern (and revisions, e.g. post-modern) arrangement that had produced our disciplines and research institutions – interfaces with the human component of our society, *other* societies, and non-human wild life that sits beyond the tamed mantle of civilisation.

This report has identified a number of areas in which substantial research investment could be made. Specifically, they include:

1. Theoretical Package:
    - rigorous analysis of the DART concept, mapping and establishing boundaries around a new class of object
    - genealogy of DARTs
    - DARTs’ relationship with similar objects (replication incompetent autonomous devices (e.g. robots), and replication-incapacitated biological devices (e.g. genetically sterile insects)

- implications for understandings of power, agency and the structuring of society and its relationship with both the environment and its technologies.
- ethical considerations of DARTs (precaution, tradeoffs between anthropocentric and ecocentric values, etc)

2. Legal Package
    - international treaty networks
    - coverage issues (more than transgenics)
    - precautious biosafety legislation that can handle the prospect of radical technological intervention for human health and environmental benefit.
3. Sociological and Political (Empirical) Package
    - micro-histories of particular DART programs
    - cultural antecedents and contexts of DART imaginations, developments and deployments, including driving factors and use of language and metaphor
    - international relations and cross-cultural issues – resolutions, conflicts, epistemic norms
    - the role, power and governance of new institutional actors, e.g. philanthrocapitalist organisations and technological solutions
    - participation in DART development and deployment

This is a modest evaluative synthesis of research and issues emerging from a burgeoning field. The implications and issues extend, however, beyond a purely academic community.

Internationally, particularly within the auspices of negotiations on the Cartagena Protocol on Biosafety, but also in other important policy domains, Norway has taken a leading, proactive stance on the governance of bioinnovations. That leadership should continue. DARTs have a strong potential for causing international dispute, most obvious in the variety of biological DARTs in preparation.

As a final recommendation, then, Norway might consider establishing a portfolio of research closely co-ordinated with its policy and foreign affairs arms.

7 Appendix 1 - Immunocontraception and its institutions

Modification of biocontrol agents by genetic manipulation, and in particular, immunocontraception vectored by a living agent, were concepts in circulation among the wildlife management epistemic community in the late 1980s and early 1990s (Tyndale-Biscoe and Jackson 1990; Tyndale-Biscoe 1991; Jolly 1993; Tyndale-Biscoe and Hinds 2007). As an idea, virally vectored immunocontraception (VVIC) was very much a child of one organisation, the Commonwealth Scientific and Industrial Research Organisation of Australia, (particularly sparked by Hugh Tyndale-Biscoe, and later Lyn Hinds), but was discussed and refined amongst a small group of scientists (internationally as well as intra-organisationally) until seed funding was procured from the Australian government in 1989 (Tyndale-Biscoe and Hinds 2007) see this reference for more detailed history on VVIC). In 1992, Australia began a well-funded and relatively high-profile collaborative research program to develop immunocontraceptive biological agents for three of its worst invasive pest species, the European fox (*Vulpes vulpes*), the European rabbit (*Oryctolagus cuniculus*), and the house mouse (*Mus domesticus*) using viral vectors. This organisation, the Cooperative Research Centre for Biological Control of Vertebrate Pest Populations, (1992-1999), was unusually successful for this kind of research program in securing a second round of competitive funding as a successor, the Pest Animal Control Cooperative Research Centre, (1999-2005).

A successor organisation, the Invasive Animal Cooperative Research Centre has emerged since 2005, although with a substantially different research program that does not include immunocontraception. Despite late-arising indications of progress, substantial investment over 14 years had not yielded a useable DART. Only the mouse program continues, but not within the Invasive Animal CRC. Recently, the head of the centre was honoured with a national award for the public communication of science. As science and technology matters go in Australia, invasive species are high-profile. The Invasive Animal CRC has New Zealand members, emerging from increasing trans-Tasman contact in the last years of its predecessor.

New Zealand researchers did, however, participate in an earlier, quite separate Australian research program that investigated ways of controlling invasive marsupial populations (e.g. over-abundant kangaroos), the CRC for Conservation and Management of Marsupials (1995-2004; (Anon. 2010a). Strategies included immunocontraception and hormonal interference, although the delivery mechanisms considered were explicitly not auto-disseminating, focusing instead on an oral (i.e. bait) delivery (Rodger year unknown). The Marsupial CRC did not, therefore, constitute a program to develop a DART.

8 Appendix 2 – Poverty, disease, failure and promise.

Malaria is currently endemic in 109 countries, a combined population of 3.3 billion people, with sub-Saharan Africa being the worst afflicted (World Health Organization 2008). WHO reports 247 million cases of malaria in 2006 alone, with around 1 million fatalities (World Health Organization 2008). Most mortality occurs in children; malaria is responsible for about 25% of deaths in children under five in areas most severely affected by the disease (Snow et al. 1999). Anti-malaria campaigns were widespread in the middle of last century; many non-tropical regions such as Sweden, Italy, and the southern USA managed to defeat the disease through intensive public health campaigns including medication of the sick and a rising standard of living, and vector control by insecticide spraying and wetland drainage (Reiter 2001; Patterson 2004; Bowden et al. 2008). History in the developing world has not nearly been so kind.

There is now good evidence of a striking overlap between persistent infectious diseases and enduring poverty (Box 4.2.1). Disease processes (vulnerability to infection, illness, elevated mortality) are thought to exist in a mutually reinforcing relationship (i.e. positive feedback loop) with socio-economic processes that impede economic growth and development (e.g. poor workforce productivity, poor educational participation/outcomes; (Bonds et al. 2009). High levels of such disease coupled with poverty form a ‘poverty trap’, each condition maintaining the other and strongly holding the afflicted community in low levels of development[38]. Recent research is highlighting the correlation of infectious disease (particularly contracted early in a child’s development) and low national scores on intelligence metrics, pointing suggestively to part of the mechanism behind the poverty trap (Eppig et al. 2010; Venkataramani 2010). Some analysis finds malaria to be the single most explanatory factor for African underdevelopment (Bhattacharyya 2009). Tackling such diseases is thus increasingly seen as a priority for development assistance within a framework of economic development as well as compassionate or ethical intervention.

Trends for malaria and other mosquito borne diseases are generally getting worse. Dengue fever particularly is attracting renewed attention (Gubler 2002). Factors behind the resurgences include population growth, changes in demographics and land use, and the erosion of public health programs and institutions under fiscal austerity programs demanded by the International Monetary Fund and World Bank (Gubler 1998; Gubler 2002; Hay et al. 2004; Stratton et al. 2008). Increased and faster global movement of people and biological entities (e.g. livestock), and the consequences of a changing climate (Shope 1991; McMichael et al. 1996; Patz et al. 1996) have worked to increase the probability of rapid global spread of infectious agents, sometimes even before a disease is detected.

Increased and faster global movement of people and biological entities (e.g. livestock) have raised the probability of rapid global spread of infectious agents, sometimes even before a disease is detected. Early (1990s) examination of the consequences of climate change highlighted the risk of vector borne disease

[38] This argument is explored with a mathematical model of disease ecology and economic development (Bonds et al. 2009). The authors find two stable state solutions for the system (i.e. community being modelled): either developed and low susceptibility to serious, endemic communicable disease, or underdeveloped and highly diseased. The dynamics of the system do not favour intermediate levels of development and disease; a smooth progressive transition from one state to the other is unlikely without structured interventions.

expanding its range (Shope 1991; McMichael et al. 1996; Patz et al. 1996), particularly in regards to increased warmth and rainfall. This raised the persistent and influential figure of the introgression of diseases we expect of poorer, equatorial nations into the territories of richer developed nations (e.g. (Feresin 2007; Lines 2007; Rosenthal 2007). Tackling the 'diseases of the poor' takes on a mantle of enlightened self interest for the global North[39].

In 1998, a new director general of the World Health Organisation launched the "Roll Back Malaria" campaign (Nabarro and Tayler 1998). Six years later, influential critics declared it a failing overpromised and underfunded campaign (e.g. (Narasimhan and Attaran 2003; Yamey 2004). It all seemed like history repeating itself, with the de-motivating memories of the 1950s and 1960s failure of the Global Programme for Malaria Eradication (Tanner and Savigny 2008; Greenwood 2009) still clear in people's minds. Expectations of success were, politely, rather modest. The notion of "eradication" of malaria was seen as naive or even taboo (Greenwood 2009).

Two things changed world opinion on this matter, and have been responsible for a new wave of money, effort and technological effort against malaria that, we can speculate, will have broader consequences for vector-borne disease in general, and hence DARTs. First, campaigns in malaria endemic states like Zanzibar other regions, focusing on insecticide-treated bednets and medical interventions targeted at the most vulnerable sectors of the human population (mothers and infants) managed to reduce malaria incidence by up to half (UNICEF and Roll Back Malaria Partnership 2007). This inspiring and instructional accomplishment, although far from a job completed, was concrete proof that substantial inroads could in fact be made against a disease that many had given up upon as intractable. It became fundamental in spurring – or perhaps validating – a new surge of optimism.

Riding on the crest of that sense of possibility came a second event, one that changed the landscape of malaria control profoundly, and perhaps marks an historical point in the history of DARTs. At a conference in Seattle in October 2007, under the spotlight of the world, Melinda Gates declared that the world should refocus and envision a world in which malaria was eradicated. The influential journal, *Science*, reported the event with an article entitled, "Did they really say… eradication?" (Roberts and Enserink 2007). Then, amid pubic spin that attempted to pull back the audacious goal to the more achievable "elimination" (see Box 4.2.2 for distinctions), the audacious goal was quickly reaffirmed by none less than the WHO and the Roll Back Malaria campaign (Greenwood 2009).

[39] Note however that a *simple* dynamic of expansion away from the equators has been discredited (Reiter 2001; Ostfeld 2009), although the notion of Southern diseases spreading North is still reasonably contemporary (McMichael et al. 2006).

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